NOV 30 1932

Vol. IV NOVEMBER, 1932 No. 1

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OFFICIAL ORGAN OF
THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE ASSOCIATION FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD,
ST. LOUIS, U. S. A.

Entered as Second Class Matter at Post Office at St. Louis, Mo.
Additional Entry at Fulton, Mo.

The Journal of Allergy

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The Journal of Allergy

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Original Articles

THE ALLERGIC ACTIVITY OF PROTEINS STERILIZED BY DRY HEAT*

BEN Z. RAPPAPORT, M.D.
CHICAGO, ILL.

INTRODUCTION

PROTEINS prepared for parenteral injection are usually sterilized by Berkefeld filtration. To prevent contamination a chemical antiseptic, usually one of the creosote derivatives, is commonly added. In pollens, however, glycerine as a preservative has gained increasing favor since it was first used by Clock.[1]

Experience in our laboratories has led to objections to the use of Berkefeld filtration and chemical sterilization as a general means for the sterilization of all proteins. The Berkefeld candle retains an unknown quantity of the protein antigen, the amount depending on the type of material and the volume filtered. The greater the amount filtered at one time the more protein retained within the pores of the candle. This is especially true in viscous substances like egg albumen. The use of chemicals in protein solutions is also objectionable, since most of them alter proteins.

The effect of heat on the activity of solutions of pollen has been studied by several workers. Black[2] boiled pollen extracts for ten minutes without diminishing their potency. Gay[3] found a solution of short ragweed pollen less resistant to heat. While its activity was diminished, it still produced skin reactions in hay fever patients after it had been heated for one hour at 100° C.

Chick and Martin[4] were able to heat dry proteins for long periods without coagulation. They demonstrated that crystalline egg albumen dried by pressing between filter papers but still containing 20 per cent moisture, could be exposed to dry heat for five hours at 120° C. without altering the solubility of the material. This observation suggested the use of dry heat to sterilize pollen before extraction, with the following questions under consideration:

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1. The temperature and time required to destroy spore bearing organisms protected by dry protein material.
2. The effect of such heat on the solubility of the protein material.
3. The effect of heat on the antigenicity of the material as demonstrated by the skin reaction in sensitive individuals and by its efficacy in the treatment of susceptible persons.

THE STERILIZATION OF DRIED EGG ALBUMEN INFECTED WITH B. SUBTILIS

The *B. subtilis* was selected because of the resistance of its spores to heat, to determine the temperature and time required for sterilization when coated by dry egg albumen. A solution of commercial egg albumen was inoculated with this organism and permitted to stand at room temperature for forty-eight hours. Smears made at the end of that time showed the presence of many spores. After the material was dried in a specially designed drier under a current of air at 40° C., it was divided into a number of half gram specimens which were used for the sterilization experiment. These were placed in an electric oven with thermostatic control at 120° C. After a primary heating period of two hours, a specimen was quickly removed every half hour, until the last had been exposed to heat for twelve hours. Each of the specimens was allowed to swell overnight in a small amount of sterile distilled water and then dissolved by the addition of 15 c.c. of sterile distilled water. No difference in the solubility of these specimens was noted in comparison to a half gram portion of unheated commercial egg albumen dissolved in the same manner. Each solution made from the heated material was plated out on agar and incubated for forty-eight hours. Colonies of *B. subtilis* were present on all the plates except those from materials heated for eleven and one-half and twelve hours. The experiment was repeated and the same results were obtained.

Because it was found impractical to leave material in for a long period of time, the experiment was repeated with the oven set at 140° C. instead of 120° C. Specimens were removed every half hour starting at the end of a primary hour of heat, until the last had been heated for three hours. The other details of the experiment were unchanged. The solubility of the heated specimens, compared to unheated egg albumen was unaltered. The *B. subtilis* was present in the cultures made except in those specimens heated for two hours or longer. The experiment was repeated, this time removing one tube every fifteen minutes starting at the end of one and a half hours of heating and ending at three hours. Again the cultures made showed growth of *B. subtilis* in all specimens heated for less than two hours and no growth in those heated for two hours or more.

THE SKIN REACTION OF SENSITIVE PATIENTS TO EGG ALBUMEN STERILIZED BY HEAT

Eight egg sensitive patients were tested with solutions of the commercial egg albumen. One solution was prepared from material heated

at 140° C. for two hours; the other from unheated material. Both solutions were diluted to a nitrogen content of 0.1 mg. per cubic centimeter. The scarifications were made on the inner and outer surfaces of the forearm at the same level with a multiple scarifier.[5] By carefully adjusting the blades and exerting uniform tension on the skin of the forearm, incisions of practically equal depth and length were made with this instrument. Further to insure the uniformity of the scarifications, the unheated material was placed over the uppermost and lowermost incisions made on the inner surface of the forearm, and the heated egg albumen over similar incisions made by the same blades on the outer surface of the forearm. The reactions were read at the end of twenty minutes. In all cases the heated and unheated materials gave the same size wheal and erythema. In three of the eight cases, itching occurred earlier and was more marked at the site of the unheated material.

THE ACTIVITY OF POLLEN STERILIZED BY DRY HEAT

Five grams of giant ragweed pollen and five grams of short ragweed pollen were placed in a desiccator over sulphuric acid for five days to insure dryness of the materials and then separately placed in dry one-half liter bottles containing glass beads. The bottles were stoppered with cotton and placed in an electric oven for two hours at 140° C. At the end of this period the pollen had changed from the original yellow color to a dark tan. Two hundred cubic centimeters of sterile buffered saline at a P_H of 6.0 was added to each of the bottles which were then closed with sterile rubber stoppers and shaken for forty-eight hours in a shaking machine. The materials were permitted to settle for four days and the supernatant fluid was carefully removed with a 100 c.c. sterile pipette. Cultures of these solutions were found sterile. The nitrogen content determined by micro-Kjeldahl was 0.0186 per cent for the giant and 0.02 per cent for the short ragweed. This is about two-thirds of the concentration that we have obtained in previous preparations of unheated giant and short ragweed pollen solutions sterilized by Berkefeld filtration. Each of the two pollen preparations were diluted to the following nitrogen concentration: 0.05 mg. N. per cubic centimeter, 0.01 mg. N. per cubic centimeter, and 0.001 mg. N. per cubic centimeter. Similar dilutions were made with giant and short ragweed pollen solutions prepared in the same manner but sterilized by Berkefeld filtration without having been previously heated.

Twenty-one ragweed sensitive patients were tested by the cutaneous method with each of these solutions, using one forearm for the heat-sterilized and the other forearm for the Berkefeld-sterilized material. The instrument used for these tests is the multiple scarifier previously mentioned, the blades of which were carefully adjusted to produce, as nearly as possible, cuts of the same length and depth. In addition, to make the tests more nearly comparable, the same dilutions of the heated and unheated pollen solutions were placed over cuts made by the same

blade, at a similar level on each forearm. Using the instrument in this manner we found that reactions of equal intensity could be produced in a sensitive patient when one concentration of pollen solution was placed over several scarifications made by the same blade. The reactions were outlined in ink at the end of twenty minutes and transferred to moist blotting paper for comparison. The readings were interpreted in terms of plusses for the convenience of charting.

As will be noted from Table I, in 14 of the 21 patients the reactions obtained with the solutions of the heat-sterilized dry pollen were as pronounced as those with solutions of unheated Berkefeld-sterilized pollen. In 6 of the 21 they were practically as large, while only in patient No. 3 were they slightly smaller. This patient was not available for a retest. Considering the possibility of error in the transferring and reading of the reactions, it can be safely said that the skin reactions were of the same size for similar nitrogen concentrations of heated and unheated materials.

It will be noted from Table I that in 11 of the 21 patients the reaction to the short ragweed pollen was distinctly greater than that to the giant ragweed pollen, while in one no reaction was obtainable to the giant ragweed pollen in the concentrations used. Some of these patients were included in a larger group studied with C. A. Johnson.[6] The results of tests made on this latter group confirm the observation that in some ragweed sensitive patients the skin reaction obtained with short ragweed pollen is larger than that with giant ragweed pollen.*

TABLE I

THE ACTIVITY OF HEAT-STERILIZED POLLEN AS DETERMINED BY ITS EFFECTIVENESS IN THE TREATMENT OF SENSITIVE PATIENTS

One hundred and seventeen patients who reported for treatment before July 15, 1931, were chosen from private practice and from the Allergy Clinic of the Research Hospital of the University of Illinois, College of Medicine. They were divided into two groups. Fifty-seven of these, irrespective of the presence of asthma, sinus infections or previous history of treatment, were injected with pollen solutions sterilized by heat, and 60 were treated with pollen solutions sterilized by Berkefeld filtration. No chemical antiseptic was added to either material. In this work I wish to acknowledge my indebtedness to Dr. Tell Nelson, who not only used the heated material on a group of clinic patients but also on ten patients in his private practice, and submitted the data for this publication. The minimum number of injections received by any patient in each group was twelve. Almost all of the patients were given seasonal injections once a week of about 50 per cent of the maximum preseasonal dose. The average number of injections given to each patient in the

*I am aware of the conclusive work recently reported by Stull, Cooke and Chobot[7] on the biologic identity of the active substance in short and giant ragweed. I have been able to repeat the procedure of interchanging doses of giant and short ragweed (unpublished) without producing a constitutional reaction. It is possible that the skin reactivity involves processes different from the constitutional reaction.

TABLE I

SKIN REACTIONS WITH HEATED AND UNHEATED PROTEINS

	SHORT RAGWEED						GIANT RAGWEED					
CASE NO.	HEATED 0.05 MG. N. C.C.	UNHEATED 0.05 MG. N. C.C.	HEATED 0.01 MG. N. C.C.	UNHEATED 0.01 MG. N. C.C.	HEATED 0.001 MG. N. C.C.	UNHEATED 0.001 MG. N. C.C.	HEATED 0.05 MG. N. C.C.	UNHEATED 0.05 MG. N. C.C.	HEATED 0.01 MG. N. C.C.	UNHEATED 0.01 MG. N. C.C.	HEATED 0.001 MG. N. C.C.	UNHEATED 0.001 MG. N. C.C.
1	++++	+++	+++	+++	−−	+	+++	+++	++	+++	+	+
2	+++	+++	++	++	+	+	+++	+++	++	++	−−	−−
3	+++	++++	++	+++	+	+	++	++	+	+	−−	−−
4	++++	++++	++	++	−−	−−	+++	+++	+	+	−−	−−
5	++++	++++	++	++	+	+	+++	+++	++	++	±	+
6	++	++	−−	−−	−−	−−	±	±	−−	−−	−−−	−−
7	++++	++++	++	++	+	+	++	++	+	+	−−	−−
8	++++	++++	++	++	++	++	++	++	+	+	+	+
9	++++	++++	++	++	−−	+	++	++	+	+	−−	−−
10	++++	++++	++	++	+	+	++	++	+	+	−−	−−
11	+++	+++	++	+	±	±	++	++	−−	+	−−	−−
12	++	++	−−	−−	−−	−−	++	++	−−	−−	−−	−−
13	+++	++++	+++	+++	−−	−−	+++	+++	++	++	−−	−−
14	++++	++++	++	++	−−	−−	+	+	±	±	−−	−−
15	++++	++++	++	++	+	+	+++	+++	++	++	−−	±
16	++++	++++	++	++	+	+	+++	+++	++	++	−−	−−
17	++++	++++	++	++	−−	+	++	++	++	++	−	−
18	+++	++++	++	++	−−	−−	+	+	±	±	−	−
19	++++	++++	++	++	−	−	++	++	±	±	−	−
20	++++	++++	+++	+++	+	+	+++	+++	++	++	±	±
21	++	++	+	+	−	−	−	−	−	−	−	−

group treated with unheated pollen was 27.5, while the average number given each patient treated with the heat sterilized material was 21.67 injections. The average maximum dose attained was also higher in those cases receiving Berkefeld-sterilized material than in those treated with heat-sterilized material. The average maximum dose in the former group was 0.0377 mg. N., while in the latter group the average maximum dose was 0.0258 mg. N.

It is difficult to estimate the degree of relief obtained in any individual hay fever patient, unless the result is either very good or very poor. The majority of treated hay fever patients, however, do not belong to either of these clear-cut classes. Most of them state that they were only partially relieved. Their conclusions were based on a comparison with the symptoms of previous untreated seasons. Two factors of error are present which cannot altogether be avoided: the conclusions of the patient, and those of the questioner in classifying each individual. Each patient was questioned carefully during and at the end of the season to determine the degree of his discomfort. He was then classified in one of four groups: Excellent—90 per cent to 100 per cent relief; good—75 per cent to 90 per cent relief; fair—50 per cent to 75 per cent relief; poor—below 50 per cent relief. As conservative an attitude as possible was maintained in grouping the patients. The tendency was to undervalue the statement of the patient regarding his degree of freedom from symptoms and to place him in the lower classification where doubt existed. This attitude led to the designation of poor, or no relief, in all those who felt that they had had less than 50 per cent relief. Those who in untreated seasons had had severe asthma and who during this season were completely or almost completely relieved from these symptoms, but who still had moderate to severe hay fever were classified as fair.

The therapeutic results are shown in Table II.

TABLE II

THERAPEUTIC RESULTS OF CASES TREATED BY INJECTIONS

	TOTAL NO. OF PATIENTS	EXCELLENT		GOOD		FAIR		POOR	
		NO. OF PATIENTS	PER CENT	NO. OF PATIENTS	PER CENT	NO. OF PATIENTS	PER CENT	NO. OF PATIENTS	PER CENT
Unheated pollen	60	11	18.33	25	41.66	12	20	12	20
Heated pollen	57	13	22.87	16	28.07	18	31.58	10	17.56

While there is no close correspondence in the percentages of the various classes in the two groups, neither is there a great divergence in the

more general results, that is, relief in 80 per cent of the cases treated with unheated pollen, and 82.44 per cent of those treated with heat-sterilized pollen. These patients treated with unheated pollen probably received more relief than those treated with the heated material since a total of 59.99 per cent of the former group had either excellent or good results while only 50.94 per cent of the latter group had that much relief. The difference, however, is not great and may have been due to the unavoidable error in classifying so small a number rather than to the more frequent injections or the heavier maximum dose.

Because of the severity of symptoms resulting from the unusually high pollen concentration and prolonged pollenating season of the past year, the results obtained in either group cannot be closely compared with those obtained during previous seasons, either in my practice or in that of other allergists. Vander Veer, Cooke, and Spain[8] report the following percentages of satisfactory results: 1924, 77 per cent; 1925, 75 per cent; 1926, 84 per cent. This indicates that when the difference in pollen concentration during the various years is great, no close comparisons can be made of results obtained in different seasons.

DISCUSSION

The spores of *B. subtilis* in egg albumen were killed when the dried material was exposed to dry heat for eleven and one-half hours at 120° C. or for two hours at 140° C. As indicated by the skin reactions in sensitive individuals, neither the solubility nor the antigenicity of the egg albumen was altered by dry heat for two hours at 140° C. Dry giant and short ragweed pollen heated at 140° C. for two hours was shaken for forty-eight hours with buffered saline. The nitrogen content of these solutions was about two-thirds that of similarly prepared unheated pollen. The heated materials were sterile and the skin reactions obtainable with them in sensitive individuals were as large as those obtained with unheated Berkefeld sterilized ragweed pollens of the same nitrogen concentrations. A group of 57 patients were treated with heat-sterilized pollen and another group of 60 with unheated pollen, sterilized by Berkefeld filtration. The therapeutic results obtained in each group were similar.

While pollen may be sterilized by heat, when the material is thoroughly dry, without any demonstrable change in the potency of the material, this method is not to be chosen to replace Berkefeld filtration. Unless the material is thoroughly dried in a desiccator over sulphuric acid, it is likely to be charred when heated. In addition the technical difficulty is greater, and the chances for contamination in removing the supernatant fluid, after allowing the pollen to settle, are greater than in Berkefeld filtration. The method is, however, applicable to materials which, because of their highly viscous nature when in solution, make Berkefeld filtration a difficult or unsatisfactory procedure. Substances available

only in small amounts may also be sterilized in this manner when the preparation of a concentrated solution of a small volume is desired.

CONCLUSIONS

1. Spores of *B. subtilis* when dried in protein material are destroyed by exposure to dry heat at 140° C. for two hours.

2. The antigenicity of egg albumen, determined by the skin reaction in sensitive patients, is not affected by heating the dry material at 140° C. for two hours.

3. The antigenicity of pollen, determined by the skin reaction and by its effectiveness in the treatment of hay fever, is not affected by dry heat at 140° C. for two hours.

REFERENCES

1. Clock, R. O.: J. Infect. Dis. **21**: 387, 1917.
2. Black, J. H.: J. Lab. & Clin. Med. **10**: 378, 1925.
3. Gay, R. N.: J. Immunol. **11**: 371, 1926.
4. Chick, H., and Martin, C. J.: J. Physiol. **40**: 404, 1910.
5. Rappaport, B. Z.: J. ALLERGY **2**: 379, 1931.
6. Johnson, C. A., and Rappaport, B. Z.: J. Infect. Dis. **50**: 290, 1932.
7. Stull, A., Cooke, R. A., and Chobot, R.: J. ALLERGY **3**: 2, 120, 1932.
8. Vander Veer, A., Cooke, R. A., and Spain, W. C.: Am. J. M. Sc. **74**: 101, 1927.

CLINICAL EXPERIENCES WITH SYNTHETIC EPHEDRINE*†

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WHILE natural ephedrine has received wide and general application in the treatment of bronchial asthma, hay fever, and vasomotor rhinitis, there has been comparatively little attention paid in this country to the use of the synthetic drug. The application of the alkaloid ephedrine in the treatment of bronchial asthma is of comparatively recent date, having first been recommended to western medicine by Chen and Schmidt[1] in 1923. The alkaloid, however, has been known since 1887 when it was first isolated in pure form by Nagai.[2] It was first prepared synthetically by Fourneau[3] in 1904, and this synthesis was later carried out by Nagai[4] (1911) and by several others in later years.

The value of the natural alkaloid in bronchial asthma stimulated therapeutic trials with the synthetic drug, and there are a number of reports in the European literature. We are, however, not aware of any reports of clinical observations in this country. We therefore wish to report our experiences with synthetic ephedrine‡ in a series of patients with bronchial asthma, hay fever and vasomotor rhinitis.

The structure of ephedrine is such that six stereoisomers are possible: *l*-ephedrine, *d*-ephedrine, *dl*-ephedrine, *d*-pseudoephedrine, *l*-pseudoephedrine, and *dl*-pseudoephedrine. Of these, two occur in nature: *l*-ephedrine, which is the ephedrine in current use and which shall be referred to as natural ephedrine, and *d*-pseudoephedrine. The *dl* forms are optically inactive racemic mixtures. The synthetic drug used by us is *dl*-ephedrine. According to Kreitmair,[5] there is no difference qualitatively or quantitatively between the pharmacologic action of *l*-ephedrine and *dl*-ephedrine. Chen,[6] on the other hand, found that quantitatively the natural drug was more powerful than the synthetic form in the ratio of 1.33:1, and Pak and Read[7] reported a similar quantitative difference in a ratio of 1.43:1. Clinically, such a difference has not been so clearly demonstrable: for example, Berger and Ebster[8] found that the natural drug acted better in some patients and the synthetic in others. Chen and Schmidt,[9] in their excellent and comprehensive monograph on ephedrine and related substances, suggest that "of the many synthetic compounds, *dl*-ephedrine and *dl*-nor-ephedrine deserve more extensive clinical trials."

Our clinical material (Table I) was of two kinds, first, patients with

*From the Allergy Section of the Medical Division of the Hospital of the University of Pennsylvania.
†Read before the Eighth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, April 30, 1932; and before the Association for the Study of Allergy, New Orleans, May 9, 1932.
‡The preparation used was *dl*-ephedrine synthesized by E. Merck, Darmstadt and Rahway, and marketed by them under the trade name Ephetonin.

the above mentioned allergic conditions to whom the drug was administered orally, and second, patients in whom the intranasal effects were observed after the application of the drug in solution. One hundred patients received first one drug then the other for a sufficient period of time to note the effects. Another group of 60 patients received the synthetic drug alone. The records of an additional 100 patients receiving natural ephedrine alone were analyzed for purposes of comparison. Our report, therefore, is based on an analysis of the records of 160 patients who received synthetic ephedrine and 200 patients who received natural ephedrine. Of the 160 patients who received the synthetic drug, 127 had bronchial asthma or bronchial asthma combined with hay fever or vaso-

TABLE I

CLINICAL ANALYSIS (ORAL ADMINISTRATION OF DRUGS)

DIAGNOSIS	NUMBER OF PATIENTS		
	GIVEN BOTH DRUGS	GIVEN ONLY EPHEDRINE	GIVEN ONLY EPHETONIN
Asthma (allergic)	66	64	33
Asthma (infectious)	22	29	6
Hay fever	8	5	18
Vasomotor rhinitis	3	1	3
Urticaria	1	1	0
Total cases	100	100	60

motor rhinitis, 26 had hay fever alone, 6 had vasomotor rhinitis, 1 had urticaria. Of the 200 patients who received the natural drug 181 had bronchial asthma or bronchial asthma combined with hay fever or vasomotor rhinitis, 13 had hay fever alone, 4 had vasomotor rhinitis and 2 had urticaria.

Both synthetic and natural ephedrine when administered orally were given in doses of 25 mg. in capsule form three times a day. This is a smaller dose than that usually employed, 50 mg. In our experience, the smaller dose, at more frequent intervals, is less liable to produce disagreeable after-effects and seems to be practically as effective in controlling symptoms. The duration during which the drugs were given continuously varied from as little as three days to a maximum of twenty months with the synthetic drug, and twenty-four months with the natural drug. This duration depended on a number of factors, such as the duration of the symptoms, the success or failure of the drug to give relief or the occurrence of unfavorable side effects.

COMPARISON OF THE THERAPEUTIC EFFECTS OF NATURAL AND SYNTHETIC EPHEDRINE WHEN ORALLY ADMINISTERED

A comparison of the therapeutic value of the two drugs is possible in the one hundred patients who were given courses of first one drug and then the other (Table II). In each instance, the evaluation was based primarily on the patient's own opinion of the results. Both drugs failed to give relief in 16 cases (16 per cent). In one of the patients placed in this group, both drugs had to be withdrawn promptly because of the occurrence of untoward effects. Both drugs were equally successful in giving partial or complete relief in 32 cases (32 per cent). In 5 additional cases, both drugs gave equally satisfactory relief from the disease symptoms, but the natural drug was followed by unpleasant by-effects which made it less acceptable to the patients. In 15 cases (15 per cent) the ephedrine gave better results than the synthetic drug; in 2 of these, the

TABLE II

COMPARATIVE THERAPEUTIC EFFECTS

Number of patients receiving both drugs	100
No relief from either drug	16
Equal relief from both drugs	32
Equal relief, but ephetonin preferred	5
More relief from ephedrine	15
More relief from ephetonin	32

synthetic drug gave no relief at all. In 32 instances (32 per cent), the patients claimed that the synthetic drug gave better relief. This figure must, however, be discounted somewhat, and for several reasons: In some instances, the patient's opinion was probably swayed toward the synthetic drug because it was attended by less unpleasant secondary effects; in others, it may have been due to the fact that the natural drug, which had been taken for some time, was losing its effect and that a change to the synthetic drug was followed by more complete relief. In only 3 cases, however, are we quite certain that this was true. In the first of these, the natural drug was less effective after six months of use, the synthetic drug continued to be effective at the end of twelve months. In the second case, the natural drug had been used only two weeks, whereas the synthetic drug was still effective at the end of two months. In the third case, the natural drug was used for two years while the synthetic drug was used for but one month.

On the basis of these figures, it is reasonable to assume that the synthetic drug was at least as effective as the natural drug. This is in accordance with the findings of European observers. Failure or only partial success was encountered by both drugs more frequently in the infectious type of asthma. Of the 22 cases of infectious asthma, 6 cases (27.2 per cent) were not relieved by either drug, and 11 cases (50 per cent) obtained only partial relief. Of 66 cases of allergic asthma only 7

(10.6 per cent) obtained no relief from either drug, and 34 (51.6 per cent) obtained only partial relief. On the other hand, the duration of asthma prior to the use of either drug appeared to bear no relation to the effects obtained, cases of long duration reacting equally as well as those of short duration. Nor did the age of the patient influence the effectiveness of either drug.

There has been some discussion, particularly in the European literature, as to whether patients taking the natural ephedrine develop a tolerance to the drug and even as to whether the drug may be habit form-

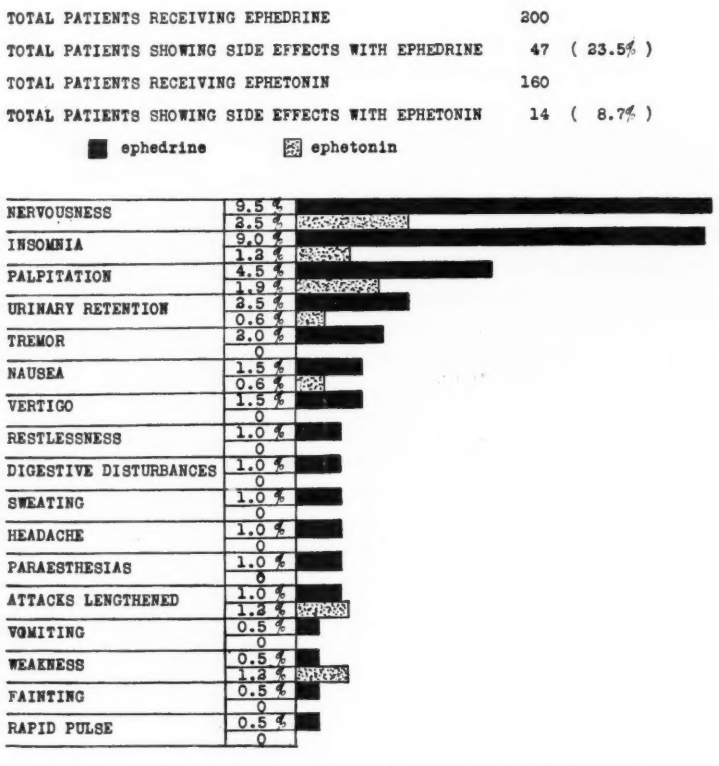
TOTAL PATIENTS RECEIVING EPHEDRINE 200
TOTAL PATIENTS SHOWING SIDE EFFECTS WITH EPHEDRINE 47 (23.5%)
TOTAL PATIENTS RECEIVING EPHETONIN 160
TOTAL PATIENTS SHOWING SIDE EFFECTS WITH EPHETONIN 14 (8.7%)
ephedrine
ephetonin
NERVOUSNESS 9.5 % 3.5 %
INSOMNIA 9.0 % 1.2 %
PALPITATION 4.5 % 1.9 %
URINARY RETENTION 3.5 % 0.6 %
TREMOR 3.0 % 0
NAUSEA 1.5 % 0.6 %
VERTIGO 1.5 % 0
RESTLESSNESS 1.0 % 0
DIGESTIVE DISTURBANCES 1.0 % 0
SWEATING 1.0 % 0
HEADACHE 1.0 % 0
PARAESTHESIAS 1.0 % 0
ATTACKS LENGTHENED 1.0 % 1.2 %
VOMITING 0.5 % 0
WEAKNESS 0.5 % 1.2 %
FAINTING 0.5 % 0
RAPID PULSE 0.5 % 0

Fig. 1.--Analysis of unfavorable side effects from both drugs.

ing. In no instance of 200 patients receiving natural ephedrine did we observe anything that might be interpreted as a drug habit. In only 3 cases did we feel was there definite evidence of diminished therapeutic effect that might be interpreted as an acquired tolerance. In none of the 160 patients given the synthetic drug did we observe habit formation or reduced therapeutic effect even though patients received the drug continuously for as long as twenty months.

Probably the most interesting and most important of our observations are those which deal with the unfavorable side effects observed after the administration of these substances (Fig. 1). It is well known that in many patients the disagreeable symptoms which follow the ingestion of

natural ephedrine are quite marked and may more than counterbalance any beneficial effects. Of our 200 patients who received natural ephedrine, 47 (23.5 per cent) experienced frank and continued unfavorable effects. The most frequent of these were nervousness (19), and insomnia (18). Others included tremor, nausea, digestive disturbances, sweating, headache, paresthesias, weakness and palpitation. The most distressing of the unfavorable effects, however, was urinary retention in mail patients, a symptom which was observed in 5 cases and which, in each instance, necessitated the immediate discontinuance of the drug. The ages of these patients were forty-six, fifty-seven, fifty-eight, seventy and seventy-four years. It is quite possible in at least 4 of these 5 that an associated prostatism played a part. It is conceivable that a mild spasm of the vesical trigone produced by either drug would fail to cause symptoms ordinarily, but in the presence of prostatism might be sufficient to produce retention of urine. In support of this view is the fact that this effect was observed by us only in males.

Synthetic ephedrine on the other hand was distinctly less prone to produce unfavorable symptoms. In only 15 of 160 patients, or 8.7 per cent, were any such untoward effects noted. They included nervousness, insomnia, nausea and digestive disturbances, and weakness, but in most instances were of a less severe degree, being usually quite negligible compared with those of the natural drug. In only one instance was urinary retention noted; in fact, two out of three patients who suffered urinary retention after the natural drug were able to take synthetic ephedrine without trouble. These findings of fewer unfavorable effects after the synthetic drug are in conformity with those of European observers. In our opinion, they constitute a decided advantage of the synthetic drug over the natural product.

In two patients, both drugs not only failed to relieve asthmatic symptoms but actually increased the patient's difficulties. Both these were patients with marked emphysema, in whom the exhibition of a vasopressor substance that is also a myocardial depressant probably had an unfavorable effect on the circulation.

It may be stated at this point, that the unfavorable effects which have been mentioned are the result of certain phases of the physiologic action of the drugs on blood pressure, the higher cerebral centers, the gastrointestinal tract and the vesical trigone. They are not to be considered as idiosyncrasies.

When the unfavorable effects after either drug were rather mild, such as slight nervousness or insomnia, it was not infrequently observed that these effects would lessen and clear up after several days to a week of continued use of the drug. If the drug was discontinued for a time and then resumed, the by-effects would usually occur again for a few days. In some instances it was then possible to minimize or avoid the by-effects by beginning with a single dose on the first day, two doses on the second and three doses a day thereafter.

True hypersensitiveness to natural ephedrine has recently been reported by Bullen, Francis and Parker,[10] who observed two cases of dermatitis medicamentosa after the oral administration of natural ephedrine. Both

TABLE III

BLOOD PRESSURE OBSERVATIONS. MAXIMUM CHANGE NOTED AFTER 25 MILLIGRAMS OF DRUG BY MOUTH

	20 ASTHMATICS	20 NONASTHMATICS
Ephedrine	minus 15	no change
	minus 6	plus 3
	no change	plus 4
	no change	plus 5
	plus 3	plus 5
	plus 5	plus 6
	plus 6	plus 6
	plus 6	plus 7
	plus 7	plus 8
	plus 7	plus 9
	plus 7	plus 12
	plus 8	plus 15
	plus 9	plus 15
	plus 9	plus 17
	plus 13	plus 18
	plus 16	plus 20
	plus 20	plus 22
	plus 20	plus 27
	plus 21	plus 29
	plus 24	plus 45
Ephetonin	no change	minus 8
	no change	minus 12
	no change	no change
	no change	no change
	no change	plus 2
	plus 3	plus 2
	plus 3	plus 4
	plus 4	plus 5
	plus 4	plus 6
	plus 4	plus 6
	plus 5	plus 8
	plus 5	plus 9
	plus 6	plus 9
	plus 6	plus 10
	plus 6	plus 10
	plus 6	plus 12
	plus 8	plus 12
	plus 8	plus 15
	plus 8	plus 15
	plus 9	plus 16

their patients gave positive patch tests to natural ephedrine but negative tests to synthetic ephedrine. Since Bullen's report we have observed one patient in whom both natural and synthetic ephedrine, when given by mouth, promptly produced a dermatitis medicamentosa, but the effect of the synthetic drug was much less severe.

Effect on Blood Pressure.—The effect on blood pressure was noted in 20 asthmatics and in 20 nonasthmatics. Each individual was given 25 mg. of natural ephedrine on one day and 25 mg. of the synthetic drug on another day, and the results were noted. In general, the effects of both drugs were more marked in the nonasthmatic than in the asthmatic individuals, and the effects were somewhat more marked with the natural drug than with the synthetic. In nonasthmatics, the natural drug produced a rise of 45 millimeters of mercury in one case, 29 in a second, 27 in a third, 22 in a fourth and from 3 to 20 millimeters in 15 others. There was no rise in one case. The maximal rise produced by the synthetic drug in nonasthmatics was 16 millimeters; there was a lesser rise in 15 cases, 2 showed no change and in 2 others there was an actual fall of pressure of 8 and 12 millimeters respectively. In the asthmatic group, natural ephedrine produced a maximal rise of 24 millimeters in one case, lesser rises in 15 cases, no change in 2, and was followed by an actual fall in pressure in 2. The synthetic drug produced a maximal rise of only 9 millimeters in the asthmatic group with lesser rises in 14 others and no change of pressure in the remaining 5. The synthetic drug in 25 milligram doses, orally administered, therefore seems to have slightly less marked effect on blood pressure than the natural drug, and this in turn is slightly less marked in asthmatics than in nonasthmatics.

TABLE IV

LOCAL EFFECTS ON NASAL MUCOSA

DIAGNOSIS	NUMBER OF CASES	
	BOTH DRUGS PRODUCED EQUAL SHRINKAGE	EPHEDRINE PRODUCED GREATER SHRINKAGE
Normals	15	—
Vasomotor rhinitis	8	—
Infectious rhinitis	10	2

Local Effects on Nasal Mucosa.—Each drug, in a 3 per cent aqueous solution was applied to an inferior turbinate and the degree and duration of the shrinkage of that structure were noted. In 15 normal individuals and in 8 patients with vasomotor rhinitis, the shrinkage was approximately equal after the two substances. In 12 cases of infectious rhinitis, there was an approximately equal effect in 10, whereas in 2 cases the natural drug gave a slightly better effect than the synthetic preparation.

In order to obtain more accurate information on this point, observations are being made on local temperature changes in the nasal mucosa as an index of the degree of vascular constriction and consequent reduction of blood supply. This is being done by means of a thermocouple and a string galvanometer, after the method devised by Liljenstrand and Gior-

dano.[11] In 12 individuals which we have studied thus far, the results seem to be the same with both drugs in 8 cases, whereas in 4 the effect of the synthetic drug is somewhat less marked.

Economic Considerations.—Three and a half years ago, when we begun our observations, the synthetic drug had a very real advantage in its lower cost. At that time the wholesale cost of natural ephedrine was $10.25 an ounce, while the synthetic drug cost only $2.25. At present both drugs are priced at about $2.00 an ounce. It is conceivable, however, that an increased demand for the synthetic drug will result in a further price reduction just as has occurred in the case of the natural drug. Finally it must be remembered that the natural drug is extracted from the crude drug which must be imported from China. The constant availability of a drug which can be produced synthetically in this country as compared with the possible uncertainty of a Chinese supply is an obvious advantage.

CONCLUSIONS

1. Synthetic ephedrine is probably equally as efficacious as natural ephedrine in the palliative treatment of asthma, hay fever, and vasomotor rhinitis.

2. With neither the natural nor the synthetic product is there any relation of the efficacy of the drug to the duration of the disease or the age of the patient.

3. The acquisition of tolerance was not noted in the case of the synthetic drug, and it was rare and almost negligible with the natural drug.

4. The effect on blood pressure by the synthetic drug when orally administered in 25 milligram doses is somewhat less than that of the natural product.

5. Synthetic ephedrine produces unfavorable side effects in less than 9 per cent of patients as opposed to over 23 per cent following the use of the natural ephedrine. These effects in our experience were usually milder after synthetic ephedrine and in only three observed cases necessitated discontinuance of the drug.

6. This relative freedom from undesirable side effects constitutes a real advantage of synthetic over natural ephedrine.

7. True hypersensitiveness to both natural and synthetic ephedrine has been observed.

8. Synthesis makes possible a constant and stable supply of the drug.

REFERENCES

1. Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine, the Active Principle of the Chinese Drug Ma Huang, Proc. Soc. Exper. Biol. & Med. **21**: 351, 1923.
2. Nagai, N.: Ephedrin, Pharm. Ztschr. **32**: 700, 1887.
3. Fourneau, E.: Etudes sur les aminoalcools: Éphédrine synthetique, J. de pharm. et chim. **20**: 481, 1904.
4. Nagai, N.: Über die Konstitution und Synthese des Ephedrins, J. Tokyo Chem. Soc. **32**: 426, 1911.
5. Kreitmair, H.: Über einen synthetischen Körper mit der Wirkung des natürlichen Ephedrins (Ephetonin), München. med. Wchnschr. **74**: 194, 1927.

6. Chen, K. K.: A Comparative Study of Synthetic and Natural Ephedrines, J. Pharmacol. & Exper. Therap. **33**: 237, 1928.
7. Pak, C., and Read, B. E.: Comparative Study of Ephedrine, Racemic Ephedrine and Pseudoephedrine, Chinese J. Physiol. **2**: 435, 1928.
8. Berger, W., and Ebster, H.: Über Ephetonin, München. med. Wchnschr. **74**: 1083, 1927.
9. Chen, K. K., and Schmidt, C. F.: Ephedrine and Related Substances, Medicine **9**: 1, 1930.
10. Bullen, S. S., Francis, N., and Parker, J. M.: Dermatitis Medicamentosa Due to Ephedrine, Reported Before the Society for the Study of Asthma and Allied Conditions, Atlantic City, April 30, 1932.
11. Liljestrand, S. H., and Giordano, A. A. S.: Personal communication.

(For discussion, see page 57.)

SKIN TESTS IN 4589 CASES OF ALLERGIC DISEASE WITH A CRITICISM CONCERNING ELIMINATION DIETS*

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SYSTEMATIC skin testing in allergic disease may be said to have had its inception in the early part of the second decade of this century, and as the realization of its accuracy and wide applicability grew so did the realization of its limitations. It is perhaps the disregard for these limitations that has permitted a certain uncritical skepticism as to its reliability to become evident in present day literature. Unfortunately, protein skin tests do not lend themselves to control by animal experimentation so that to a large extent clinical statistics have had to be relied on for their evaluation. Such statistics are notoriously subject to error especially when concerned with small groups. However, with mass statistics such as we are herewith presenting it is felt that errors can be to a large extent minimized and the accuracy of the method truly delimited.

Some 7,000 cases of allergy or suspected allergy from private and clinic practice have been gathered together and culled. Only 4,589 of these 7,000 were considered to have been sufficiently tested to be included in this study. What is meant by "sufficiently tested" will be made quite evident in our discussion of the technic of testing.

Of the 4,589 tested but 3,777, or 82 per cent, gave positive reactions. In an attempt to learn what influences thus limit the reactivity of allergic individuals, in other words to attempt to determine why two out of every ten allergic individuals do not react, two factors must be considered, first the technic of testing and second the allergic individual.

THE INFLUENCE OF METHOD ON THE ACCURACY OF RESULTS OF PROTEIN SKIN TESTING

Protein skin reactions represent a fortunate local manifestation of a constitutional state. "Fortunate," because, as will be demonstrated, by far the greatest number of sufferers from this constitutional state, which we call allergy, give such skin reactions and such skin reactions give sufficiently specific (and accurate) information to permit rational treatment.

What discredit has fallen upon the specificity of protein skin reactions is derived mainly from one source. This is that in the hands of many, skin tests to food proteins have proved unreliable either as a means of diagnosis or as a basis for treatment. We feel that this may be traced to three factors, viz., a lack of proper materials, accurate methods, and experienced interpretation in performing skin tests.

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*Read before the General Medicine Section of the California Medical Association at the sixty-first annual session, Pasadena, May 2 to 5, 1932.

It is not our purpose here to enter into the minutiae concerning these factors. Suffice it to say as regards materials that the proteins used must be absolutely trustworthy. So insistent are we on this point that we have turned to the manufacture of these for our own use, having found commercial preparations unreliable. Especially is this true with the food proteins.

Of the 3,972 patients who were tested to food proteins 2,152, or 54 per cent gave positive reactions. This includes many tests made before we began to use the intradermal method. Since that time 70 per cent of our patients give positive skin reactions to food proteins. This confirms the statement not only that the intradermal method is more sensitive than the scratch but also that one may expect seven out of every ten allergic patients to react to food protein.

In all, we have performed 564,353 individual food protein tests averaging 104 tests with 17 positive reactions to each patient, thus bringing out the fact that if the whole range of the dietary proteins is thoroughly tested out one may expect enough positive specific reactions to institute rational dietetic treatment. Here we have a definite point of departure for such treatment, elimination on a sound basis, individualized and controllable. However, it must be recalled that only by the utilization of the most comprehensive group of food test proteins available can we reliably care for our patients in this way, and realizing this we now test every allergic patient to more than 200 food substances. This is what we mean by "sufficiently" tested.

As to methods, we rely mainly on the intradermal test after making certain by the scratch test that intradermal tests will not prove too dangerous. Of all the methods of testing the intradermal is the most sensitive, reliable and simple. It is, however, also the most dangerous in the possibility of constitutional reactions and in difficulty of interpretation. Difficulty of interpretation has been a stumbling block and a source of discouragement to many, especially those who do not follow one of the first principles of therapy in allergy, i. e., to interpret and correlate the skin reactions with the clinical history and the therapeutic response.

THE INFLUENCE OF THE ALLERGIC INDIVIDUAL ON THE RESULTS OF PROTEIN SKIN TESTING

Throughout this discussion of the influence of the allergic patient on the results of protein skin testing it must be emphasized that we are using the skin tests to determine the causal agent in individuals known to be allergic and not to diagnose allergy in individuals suspected of being allergic. Otherwise our statistics would be of no significance.

Positive heredity in the production of the allergic constitution is a well-established fact. Fifty-eight per cent of the individuals tested in this series gave a positive familial history. The question arises, does this influence the reactivity of such individuals?

As may be seen from Table I a positive hereditary history results in 83 per cent of positively reacting individuals, whereas a negative hereditary history results in 78 per cent. It therefore is quite obvious that although the allergic individual may owe his peculiar make-up to his forbears, yet one cannot predicate on this basis that he will or will not give positive skin reactions. This is consistent with the fact that neither the type of allergic manifestation nor the particular substances to which an individual is sensitive is influenced by heredity.

TABLE I

INFLUENCE OF HEREDITY ON SKIN REACTIONS

	POSITIVE HEREDITY	PER CENT	NEGATIVE HEREDITY	PER CENT
Positive reactions	2090	83	1757	78
Negative reactions	400		480	

Table II was prepared to show what influence the age of the patient at the time of testing might have on his reactivity. As is evident from this table, at no age does the reactivity drop below 60 per cent. In fact in most age groups one may expect at least eight out of every ten allergic individuals to give positive skin reactions.

TABLE II

INFLUENCE OF AGE AT WHICH PATIENT WAS TESTED ON REACTIVITY

AGE TESTED	NUMBER OF PATIENTS TESTED	POSITIVE REACTIONS	PER CENT
Under 1 year	67	55	82
1 - 10 years	1,422	1,264	88
11 - 20 years	532	463	87
21 - 30 years	731	598	81
31 - 40 years	797	647	81
41 - 50 years	506	377	74
Over 50 years	443	271	61

The findings in Table III which show the influence of the age of onset on the reactivity of the skin tends to confirm the findings of Table II, despite the fact that it has often been stated that increasing age or a late onset of the manifestations of allergy is seldom associated with positive skin reactions.

Table IV demonstrates the influence on the skin reactivity of the duration of the disease. Perhaps in no other of these tables is the fact so strikingly brought out that one may expect positive skin reaction in rather more than eight out of every ten allergic individuals. A per-

sistently lower percentage than this calls for investigation of method and interpretation.

TABLE III

INFLUENCE OF AGE AT WHICH PATIENT DEVELOPED SYMPTOMS ON REACTIVITY

AGE OF ONSET	NUMBER OF PATIENTS TESTED	POSITIVE REACTIONS	PER CENT
Under 1 year	645	566	87
1 - 10 years	1,621	1,450	89
11 - 20 years	620	520	83
21 - 30 years	870	679	78
31 - 40 years	493	368	75
41 - 50 years	221	149	62
Over 50 years	119	45	38

One more factor in regard to the influence of the patient on skin reactivity must be mentioned, and this refers to the site and the time chosen for testing. Skin reactivity varies in different areas of the body

TABLE IV

THE EFFECT OF THE DURATION OF SYMPTOMS ON SKIN REACTIVITY

DURATION OF SYMPTOMS	NUMBER OF PATIENTS TESTED	POSITIVE REACTIONS	PER CENT
Under 1 year	427	342	80
1 year	452	386	85
2 years	433	367	85
3 years	421	354	84
4 years	312	274	88
5 years	293	256	88
6 years	244	200	82
7 years	197	182	92
8 years	164	148	90
9 years	115	96	84
10 years	203	172	84
11 years	59	50	85
12 years	92	72	78
13 years	51	42	82
14 years	54	47	87
15 years	106	84	79
16 years	43	38	89
17 years	26	21	81
18 years	39	35	89
19 years	17	14	82
20 years	113	91	80
21 - 30 years	289	226	78
31 - 40 years	128	103	80
41 - 72 years	77	60	78

and in the same area at different times. We have found that when the skin of the outer aspect of the upper arm is non-sensitive the skin on the back will often give good reactions and that negative tests at one sitting will be positive at a later time. For this reason, as we have frequently

pointed out, a patient giving negative reactions must be repeatedly tested until certain that positive skin reactions are unobtainable.

SKIN TESTS AND ELIMINATION DIETS

In the skin tests we have a marvellously efficient diagnostic method as such things go in medicine. It is with considerable surprise therefore that we see arising in the field of allergy the method of diagnosis by the elimination diet. Here we find an adjunct of useful purpose raised from its proper place as an adjunct to one of prime if not supreme reliance. Elimination has an impregnable place in the therapeutics of allergy. However, when it is used for diagnosis or when used for therapeutics without previous skin tests, it is open to considerable criticism. Just as skin tests have their limitations so do elimination diets, and that these limitations are considerable makes it all the more important to be aware of them. The lack of knowledge concerning the limitations of elimination diets and the insidious appeal of what superficially appears to be not only a practical but a simple method of diagnosis and treatment probably explain the popularity of the method. It is for this reason that the following critique is given.

The elimination diet does not eliminate, for complete elimination means starvation. And in another sense it does not eliminate, for unless we have also eliminated pollens from the air and epidermals, etc., from the environment how can we say that the patient is being assaulted by no offending substance? One is as important as the other, and yet it is only foods that are eliminated by the elimination diet, and individuals who are sensitive to foods alone are extremely rare. Our statistics show only one patient in one hundred as being sensitive to foods alone. Thus, even by the use of elimination diets the necessity still remains for testing to pollens and epidermals or we shall miss the diagnosis in ninety-nine out of one hundred patients.

Because many gastrointestinal symptoms or so-called migrainous headaches are relieved by elimination diets, it is argued that they must be allergic in origin, the fact being lost sight of that many nonallergic gastrointestinal symptoms and headaches may also be relieved by change in diet. This creates the fallacy becoming so evident in our literature that gastrointestinal symptoms or headaches are much more commonly caused by allergy than the facts warrant. As a matter of fact, allergic gastrointestinal symptoms and headaches are seldom if ever present without one or the other of the common and easily recognizable allergic syndromes such as asthma, hay fever, urticaria, etc., being also present. This emphasizes the fact that the diagnosis of allergy can practically always be made from the clinical findings, leaving but little excuse for the use of elimination diets to make such a diagnosis.

The cumbersomeness of the method is obvious. It not only is more time consuming than the most elaborate and prolonged skin testing pro-

gram but also subjects the patient to a prolonged period of dietetic juggling which few have the desire or ability to carry out.

It gives many practitioners a false sense of being armed with a reliable diagnostic and therapeutic instrument. With its failure they are left unable to cope with the allergic problem. Because of the insidious destruction of their belief in the efficacy of skin testing they are prone to lose their belief in the whole theory of allergy.

CONCLUSIONS

1. Regardless of the heredity, the age of onset, the age when tested or the duration of symptoms, 80 per cent of allergic patients should give positive reactions, and

2. Seventy per cent should react positively to foods and any results lower than this may be traced to

3. Promiscuous testing of nonallergic individuals, the use of unreliable proteins, the lack of persistence and completeness in testing, the inefficiency of the methods of testing and the failure to interpret reactions properly and to correlate them with the clinical history. From which it may be concluded that

4. Elimination diets as a sole reliance for diagnosis or treatment are unnecessary and frequently lead to fallacious conclusions, and finally that

5. Elimination on the basis of skin tests is a rational and reliable point of departure in the treatment of allergic disease.

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THE DEVELOPMENT OF SENSITIVENESS IN AN ALLERGIC PERSON

A Case Report

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IT IS generally agreed that allergic individuals have the tendency to become sensitive and frequently the substances to which they react are those to which they have been repeatedly exposed. It is common knowledge that an allergic person may develop clinical sensitiveness to one substance after another, but not often is it possible to watch the development of such sensitiveness in a patient who previously had been shown not to be sensitive both by skin tests and by clinical trial. Such an opportunity was afforded as is shown in the following case report.

Mrs. R. A., aged thirty-two years, married, at present employed in a beauty parlor, was referred to me on October 17, 1930, with a diagnosis of bronchial asthma. She stated that as a child she had a wheezing type of respiration under various circumstances but that it never gave her any particular trouble and she paid no particular attention to it. For the past several years she had had attacks of asthma which might come on at any time of the year but were, probably, more frequent in the spring and fall. These attacks seldom lasted more than one day, and she had paid so little attention to them that she did not know of any circumstance which might bring them about except that she did believe that damp weather probably aggravated the situation, and that she was worse in hot weather than in cold. She was unable to give any more definite information than this about her previous attacks.

On the first of January, 1930, she went to work in a beauty parlor, and her duties consisted chiefly of giving orris root shampoos. She found promptly that handling the orris root brought about a good deal of dyspnea with some unproductive cough together with some blocking of the nose. She had little or no sneezing and very little nasal discharge. The edema of the nasal mucous membrane gave her some trouble, and dyspnea and cough were sufficient to call her attention to the situation and she decided that her symptoms were due to the orris root. This was abandoned and she began the use of buckwheat flour.

For ten months she remained entirely free of all symptoms referable either to her nose or to her chest. She then developed dyspnea and cough which became progressively worse until at the time I saw her she had become unable to work, and had been having a good deal of asthma both day and night. She had typical asthmatic râles over both lungs and an occasional extrasystole. Her blood pressure was 115 systolic, 85 dias-

tolic. Physical examination was otherwise practically normal. Skin tests gave a 3 plus reaction to orris root and 4 plus reaction to buckwheat flour, the scratch technic being used. There were no other reactions to any foods, pollens, or epidermals.

She was advised to remove buckwheat flour from the shop and substitute rye flour which she stated could be used in her work and to which she gave no skin reaction. This was done at once and she remained entirely free of all allergic symptoms until the latter part of November, 1931, at which time she returned complaining of asthmatic breathing which had become so severe that she had to give up her work. Skin tests done at this time showed marked reactions to orris, buckwheat, and rye flour; all others were negative. At this time she was advised to stop the use of rye flour and substitute barley or rice flour, both of which were negative to scratch test. She changed to barley flour at once, her symptoms very promptly subsided and there has been no recurrence to date.

DISCUSSION

This patient had a sensitiveness to orris root which manifested itself immediately after exposure to it in large amounts. She was not sensitive to buckwheat flour, and more than nine months were required for a clinical sensitiveness to develop. She was not sensitive to rye flour and more than a year was required for the sensitiveness to develop. Eight months have elapsed since she began the use of barley flour and she has so far remained free of symptoms. Here we have an illustration of development of sensitiveness to substances to which the patient is successively exposed. Both clinical evidence and negative skin tests indicate that the sensitiveness did not exist prior to the time of exposure except in the case of the orris root.

AN ESTIMATE OF THE KETOGENIC DIET IN BRONCHIAL ASTHMA*†

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DURING the past few years, the ketogenic diet and other forms of acid therapy have been advocated for the treatment of allergic conditions. Tiefensee[1] found the ketogenic diet effective in the treatment of bronchial asthma, as did Peshkin and Fineman,[2] who, however, worked only with children. Barborka[3] used it with success in migraine. Beckmann[4] assembled considerable clinical data to support his theory that allergy is associated with an alkalosis, and claimed good results in treating hay fever with nitrohydrochloric acid. Bray,[5] who found hypochlorhydria in asthmatic children, advocates the use of hydrochloric acid in these cases. Moreover, hydrochloric acid is commonly used in the treatment of urticaria.

Although various reasons have been assigned to explain the effectiveness of acid therapy in allergic conditions, very little experimental data are available to substantiate them. Tiefensee[1] studied the CO_2 combining power as well as the P_H of the blood in asthmatic individuals and found that during an asthmatic paroxysm the CO_2 and P_H values were at the limits of normal toward the alkaline side or were actually elevated. He maintained, therefore, that an asthmatic attack is associated with an alkalosis and that acid therapy is indicated. The inhalation of 5 per cent to 8 per cent CO_2 proved to be effective in controlling paroxysms.

McConnell, Weaver, and Alexander[6] studied the behavior of histamine wheals in dogs under the influence of acidosis and of alkalosis. Previously they had shown what wheals induced in man both by histamine and by allergens responded alike, and that histamine wheals in dogs were comparable to those in man. They found that during acidosis the size of histamine wheals was markedly diminished, whereas during alkalosis quite the opposite occurred and the wheals were greatly increased. This is illustrated in Table I.

A localized edema such as is represented by a histamine wheal is one of the essential lesions of allergy and occurs in the bronchi during an asthmatic attack. From the above experiments, it seemed plausible to expect a diminution of the bronchial edema of asthma if a sufficient degree of acidosis could be induced. The effect of the administration of a ketogenic diet was therefore investigated.

It was appreciated that in bronchial asthma where relief is secured by

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†Read before the Tenth Annual Meeting of the Association for the Study of Allergy, New Orleans, May 8, 1932.

various measures, it became necessary to select cases for study and to observe them over a comparatively long period of time. Morever, it is difficult to maintain a ketogenic diet with its very low carbohydrate and high fat content, without expert dietetic supervision and cooperation of the patient. To meet these conditions, the study of a small series of cases was undertaken in the Jacob Porter Tirrill metabolism ward of Barnes Hospital, where ideal conditions for such investigations exist.

Patients with bronchial asthma admitted to the general service, who did not respond to routine treatment after a period of one to two weeks, were transferred to the metabolism ward. There the same diet that they had previously received was continued for a few days. If asthma con-

TABLE I

THE EFFECTS OF CHANGES IN CO_2 COMBINING POWER OF THE BLOOD ON THE SIZES OF WHEALS

DATE, DOG NO. AND WEIGHT	TIME A. M.	CO_2 COMBINING POWER VOLUMES PER CENT	SIZE OF HISTAMINE WHEALS SQ. CM.	COMMENT
March 18, 1931. Dog 5. Weight approximately 5 kilos	10:00	60	0.8	
	10:15			6.0 grams NH_4Cl in 200 c.c. water given in stomach
	10:30		0.9	
	10:45	47	0.5	
April 5, 1931. Dog 9. Weight approximately 7 kilos	11:00	59	1.0	
	11:15			6.0 grams $NaHCO_2$ in 200 c.c. water given in stomach
	11:30		1.2	
	11:45	78	1.6	

Histamine = Histamine acid phosphate 1 to 2,000 dilution.

tinued, it was felt that environmental factors in the metabolism ward played no beneficial part and a ketogenic diet was begun. A similar study was made in single rooms in the private corridor on two patients whose diet was controlled from the kitchen of the metabolism ward. Frequent examinations of the urine for the presence of ketone bodies, and occasional estimations of the CO_2 combining power and of the P_H of the blood were made. The results of this study are described in the following case reports:

CASE 1.—S. B., colored male, a laborer, thirty-five years of age. Entered Barnes Hospital October 7, 1931.

Chief Complaint.—Asthma.

Family History.—Two of his children have hives after eating particular foods. There is no antecedent history of allergy.

Past History.—Usual childhood diseases and mild influenza in 1918 were the only illnesses recalled. For the past two years the patient has had hives of unknown cause, off and on.

Present Illness.—Three weeks before admission the patient began to have choking spells lasting fifteen to twenty minutes. These were associated with wheezing and gradually grew more severe and more frequent. They came on at night and were associated with the production of thick gelatinous sputum. The patient could identify no immediate cause for these spells.

Physical Examination.—The essential findings were limited to the chest, where typical asthmatic breathing presented.

Laboratory Findings.—The blood count was normal excepting for an eosinophilia of 5 per cent. Sputum examination showed many eosinophils. Skin tests to many foods and inhalants gave no definitely positive reaction.

On a routine antiallergic régime the symptoms disappeared. The patient remained in the hospital seventeen days and was discharged improved. He returned to the hospital November 14, 1931, with a history that soon after going home the asthmatic attacks reappeared. Although he complied with the instructions given on leaving the hospital, he could get no relief. He was readmitted, and while on the general service under routine treatment he did not improve, having asthmatic attacks persistently. These could be relieved for a time by adrenalin. The patient was transferred to the metabolism service for the purpose of testing out the ketogenic diet. He was placed on a daily ration of approximately 50 grams of protein, 250 grams of fat, and 20 grams of carbohydrate. Ketone bodies promptly appeared in the urine and improvement soon began. Within twelve days the patient was asthma free.

Inasmuch as the ketogenic diet is very low in carbohydrates, essentially no wheat is included. In order to determine whether relief was secured by the elimination of wheat, a general diet was permitted but without wheat. The patient remained free from asthma. With the introduction of a full diet, symptoms promptly returned. A ketogenic diet with wheat added was then instituted, and although ketone bodies appeared in the urine, the patient became distinctly worse. Finally, he was relieved once more by the elimination of wheat. No other precautions were then necessary to keep him free from asthma. (Chart 1.)

In this case, it is apparent that the ketogenic diet was merely a conveyance for administering a wheat-free diet and that ketosis had no effects on symptoms.

In the following charts, the degree of asthma was roughly estimated by the daily amount of adrenalin necessary to keep the patient comfortable.

Case 2.—F. F., white male, a lawyer, fifty-five years of age, entered Barnes Hospital on November 15, 1931.

Chief Complaint.—Asthma.

Family History.—Negative for allergy.

Past History.—There was no significant illness until three years before onset of asthma when a severe vasomotor rhinitis developed. This did not respond to local treatment, which was the only remedy offered.

Present Illness.—The onset began four years before admission with a typical asthmatic attack, following physical exercise. This attack was repeated several times during the first year, and adrenalin always gave prompt relief. The asthmatic paroxysms then became very frequent and severe, until a constant intractable asthma was established. No relief

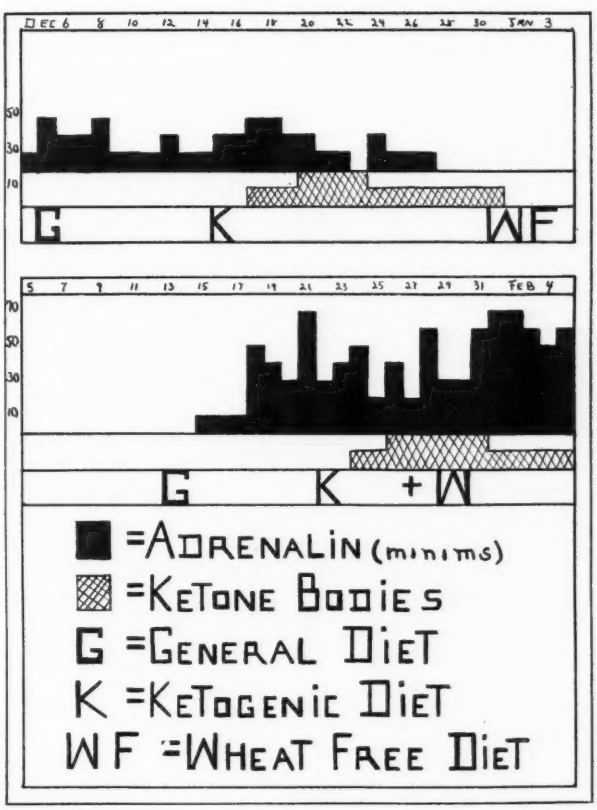

Chart 1

was secured from specialists, climate, sanitoria, or patent medicines. On entering the hospital, the patient had been taking more than 200 minims of adrenalin and one and one-half grains of morphine daily. He had developed a marked nervousness and irritability. The slightest emotional disturbance would precipitate an attack.

Physical Examination.—The significant findings were marked undernourishment, a boggy nasal mucous membrane, an extreme degree of emphysema, and typical asthmatic breathing.

Laboratory Findings.—Skin tests were positive to several foods and inhalants. A blood eosinophilia of 16 per cent was present. The sputum

was gelatinous and loaded with eosinophils. Blood CO_2 combining power before ketogenic diet was 56 volumes per cent; with ketosis it was 52 volumes per cent.

A diet in which foods giving positive skin reactions had been eliminated was given for two weeks. During this time, morphine was withdrawn.

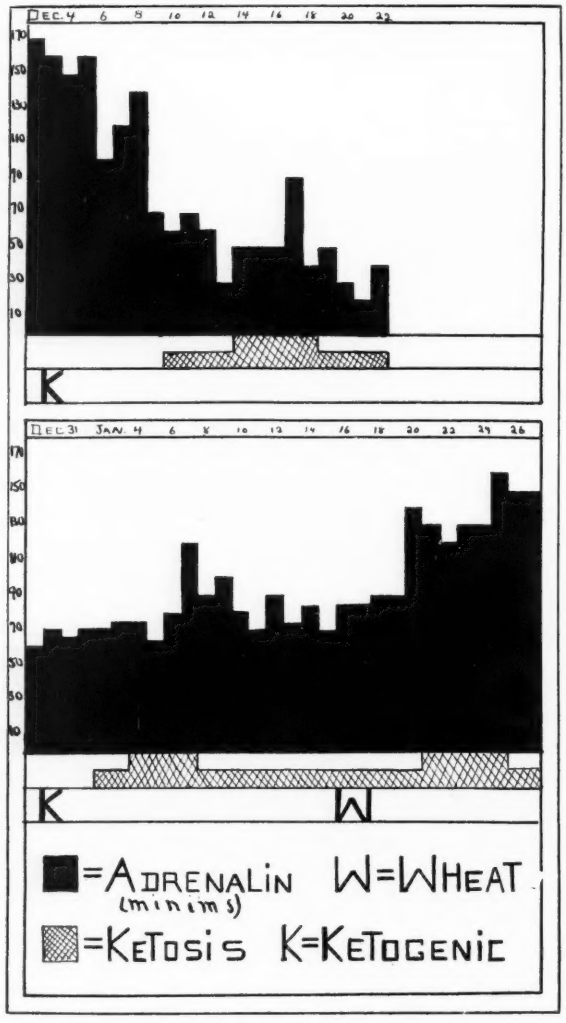

Chart 2

There was no appreciable effect on the asthmatic paroxysms. A ketogenic diet was begun (Chart 2), and although it took several days for ketosis to develop, improvement began just before ketone bodies appeared in the urine. The patient became much interested in this "new remedy" and was hopeful of results. Improvement was striking, and there were days when but 20 to 30 minims were necessary to control attacks, which had greatly

diminished in intensity. He went home for Christmas and took a nurse who had been instructed in the preparation of the diet. While at home he became much upset over his business and family affairs. He returned to the hospital with considerably more asthma, and ketosis had disappeared. A rigid ketogenic diet was immediately reinstituted, and although ketone bodies became abundant in the urine, the patient steadily became worse. He then refused to continue with the diet unless bread were added. This was done, but by manipulation a ketonuria was still maintained. Discouragement, irritability, and unreasonableness superceded his previous optimism, and the asthmatic paroxysms gradually increased.

In this case there was distinct improvement during the initial maintenance of the ketogenic diet, whereas it later had no effect. The early improvement is attributed to emotional and psychic factors which played such an important part in this case, rather than to any direct influence of the diet itself.

CASE 3.—G. C., a white female, a housewife, thirty-six years of age, entered Barnes Hospital December 16, 1931.

Chief Complaint.—Asthma.

Family History.—Father had hay fever. One sister had asthma.

Past History.—The patient had eczema in infancy and hay fever for the past sixteen years. She had been subject to repeated attacks of bronchitis.

Present Illness.—Asthmatic attacks began eleven years before admission and at first were associated with hay fever, and occurred only in the late summer. For the past six years asthma had been present all the year round. In the winter it usually had followed bronchitis, and the only periods of freedom recently were in the early summer months. The presenting attack had persisted for four months.

Physical Examination.—The essential findings were evidences of vasomotor rhinitis, a pronounced emphysema, typical asthmatic breathing, and many moist râles indicative of bronchitis. The temperature ranged from 99° to 101°.

Laboratory Findings.—W.B.C. 14,500, polymorphonuclears 79 per cent, eosinophiles 7 per cent. The sputum was mucopurulent and contained both pus cells and eosinophiles. Skin tests gave a marked reaction to ragweed and lesser reactions to several inhalants and foods. The blood P_H was 7.38 before ketogenic diet was given, and 7.38 after the diet. X-rays of the chest revealed evidences of chronic bronchitis.

A general diet was instituted on admission with no beneficial effect. After one week a ketogenic diet was begun and a ketosis established continuously for five weeks. There was no essential improvement. The patient had difficulty in taking the diet and finally began to lose weight, and the asthma increased. Carbohydrates were then added and paroxysms persisted. (Chart 3.)

In this case, where infection evidently had been superimposed upon an allergic asthma, the ketogenic diet had no appreciable beneficial effect.

CASE 4.—L. S., a white female, a salesgirl, twenty-two years of age, was admitted to Barnes Hospital on December 22, 1931.

Chief Complaint.—Asthma.

Family History.—Her maternal grandmother, and mother, each had asthma. One brother had hay fever.

Past History.—The patient had eczema off and on for years. Certain foods had caused immediate hives. She had been generally in good health.

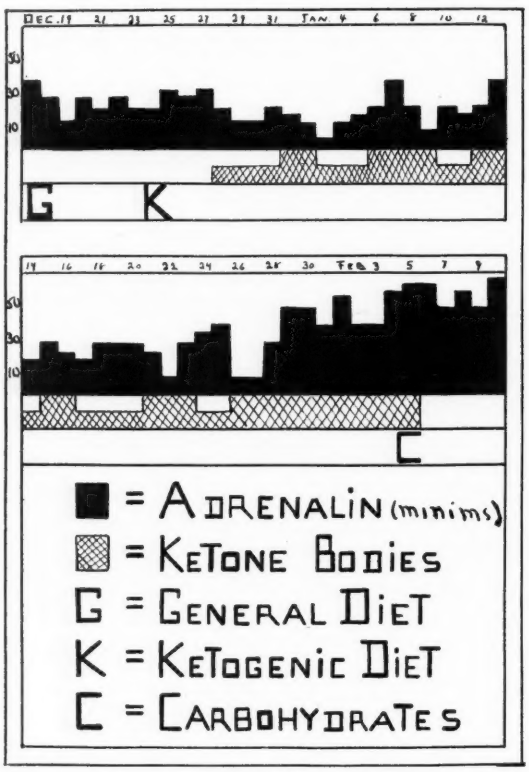

Chart 3

Present Illness.—Asthma had occurred off and on for the past several years, but it usually responded to treatment. The present attack began about one month before admission and became sufficiently severe to be completely incapacitating.

Physical Examination.—The essential findings were negative with the exception of the chest, where typical asthmatic breathing presented. There was but little emphysema.

Laboratory Findings.—A blood and sputum eosinophilia were present. Skin tests gave many doubtful reactions to both foods and inhalants, but no pronounced response.

On a general diet, asthma persisted. A ketogenic diet was followed by considerable improvement at first, but attacks gradually became more severe again. The ketogenic diet was discontinued and carbohydrates were added. This was followed by an increase in frequency and severity of attacks. Finally a Rowe diet was given with immediate and continued relief.

This patient evidently was sensitive to foods, although skin tests did

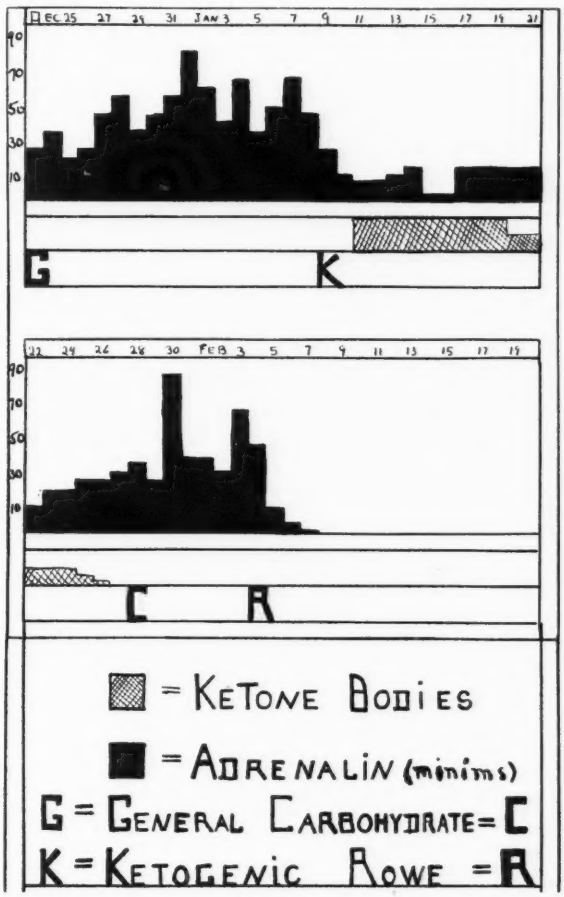

Chart 4

not reveal the offending factor. Food elimination was far more effective in controlling asthma in this instance, as in Case 1, than was the ketogenic diet.

DISCUSSION

The four case reports herewith presented are representative of a series of nine patients similarly studied. In no instance was it evident that ketosis had a pronounced beneficial effect on the severity or duration of the asthmatic paroxysms. In a few cases, some improvement was noted,

but not enough to warrant the institution of a ketogenic diet, which is difficult to maintain.

Theorectically, a ketogenic diet is indicated in allergic conditions, inasmuch as localized edema is much reduced during an acidosis. The establishment of a ketonuria, however, is associated with little, if any, change either in the CO_2 combining power of the blood or in its P_H value. Consequently, the acidosis induced is not great and doubtless is insufficient to affect the allergic lesion.

It should be noted that all the patients studied were adults. According to Peshkin and Fineman's experience, a ketogenic diet has a beneficial effect on the asthma of children.

SUMMARY

1. Nine cases of bronchial asthma were treated by a ketogenic diet. No pronounced beneficial results were noted.

2. The failure of this treatment is attributed to the fact that the acidosis induced is too mild to affect the allergic lesion.

REFERENCES

1. Tiefensee, K.: Experiments on the Acid-Base Equilibrium in Bronchial Asthma, Deutsch. Arch. f. klin. Med. **165**: 265, 1929.
2. Peshkin, M. M., and Fineman, A. H.: Asthma in Children; Rôle of Ketogenic and Low Carbohydrate Diets in Treatment of a Selected Group of Patients, Am. J. Dis. Child. **99**: 1240, 1930.
3. Barborka, C. J.: Migraine: Results of Treatment by Ketogenic Diet in 50 Cases, J. A. M. A. **95**: 1825, 1930.
4. Beckmann, H.: Allergy Considered as a Special Type of Alkalosis, J. ALLERGY **1**: 468, 1930.
5. Bray, G. W.: The Hypochlorhydria of Asthma in Childhood, Quart. J. Med. **24**: 181, 1931.
6. McConnell, F. S., Weaver, W. K., and Alexander, H. L.: Observations on the Formation of Wheals. V. The Effects of Variation of the CO_2 Combining Power of the Blood on Histamine Wheals, J. Clin. Investigation **11**: 205, 1932.

(For discussion, see page 63.)

POISON IVY. A NEW METHOD OF IMMUNIZATION

Preliminary Report*

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PRESENT day knowledge of the prevention and treatment of poison ivy is aptly summarized by Andrews[1] when he says: "innumerable attempts have been made to immunize against dermatitis due to poison ivy by ingestion of the leaves, oral administration of the tincture and by hypodermic injection of the toxic extract. None of these measures has definite value either as a preventive or as a cure, and sometimes they seem to have a detrimental effect."

In 1916 Duncan[2] first advocated the ancient folk remedy of chewing the leaves of the plant. This was followed by violent gastric reactions. Later Strickler[3] proposed the oral administration of the alcoholic extract of the leaves. An injection method of treatment advocated by Schamberg[4] (used also prophylactically) and modified by Clock,[5] Spain and Cooke[6] has likewise been criticized by Krause and Weidman[7] as ineffective. Templeton[8] has recently stated that the injection method neither prevented nor cured poison ivy dermatitis.

In view of these contradictory reports, it occurred to me that it might be possible to immunize the skin directly by subjecting the patient's skin to contacts with small increasing doses of an extract of poison ivy. This was accordingly done in the following case.

M. T., male, aged twenty-seven years, a broker by occupation, was first seen in May, 1931. At this time he gave a history of having had poison ivy annually for about ten years. He suffered from a dermatitis throughout the entire year. Although pruritis was more or less constant, the acute skin lesions became prominent in the spring and summer months. His avocation of Boy Scout leader caused him to go into the country almost every week-end throughout the year, and each time he received a reexacerbation of ivy dermatitis. A day or two after exposure, acute vesicular lesions would appear, most marked on his arms and legs. Invariably four to five days after exposure, he would have a fresh crop of milder lesions similar in character. In other respects his history was entirely negative from both a general and allergic viewpoint.

The patient stated that he had received the injection treatments repeatedly for several years, both as a preventive and as a cure, but without deriving any benefit. The injections often resulted in increased discomfort, pruritis, and even local hemorrhagic extravasations. Similar symptoms following the injection treatment had been noted by Krause and Weidman.[7]

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*From the Adult Allergy Clinic of Mt. Sinai Hospital, New York City.

A patch test was done with the tincture of *Rhus toxicodendron*. This resulted in a localized, vesicular eruption within twelve to eighteen hours. The reaction persisted for days. Treatment with oral administration of very small doses of the tincture of *Rhus tox.* was instituted. This was gradually increased until he was able to tolerate the tincture in large amounts. His dermatologic condition showed no evidence of improvement after this therapy. In the winter the patient still continued to complain of generalized pruritis. On January 29, 1932, after discussing with him the need for trying some other method of treatment, the following procedure was outlined:

It was decided to employ a daily bath of five minutes' duration in a measured quantity of water to which a measured quantity of the tincture of *Rhus tox.* had been added. A minute initial dose of the medication was used on the first occasion in order to avoid a reaction, only one drop of the tincture of *Rhus tox.* being added to ten gallons of water, and approximate dilution of 1:600,000 of the alcohol extract. Subsequently the schedule followed was as follows:

TINCT. RHUS TEX.

1st Week	2nd day	—	4 drops	in 10	gallons of water.
	3rd day	—	8 drops	in 10	gallons of water.
	4th day	—	10 drops	in 10	gallons of water.
	5th day	—	15 drops	in 10	gallons of water.
	6th day	—	30 drops	in 10	gallons of water.
	7th day	—	30 drops	in 10	gallons of water.
2nd Week	8th day	—	30 drops	in 9	gallons of water.
	9th day	—	30 drops	in 9	gallons of water.
	10th day	—	30 drops	in 9	gallons of water.
	11th day	—	60 drops	in 9	gallons of water.
	12th day	—	60 drops	in 9	gallons of water.
	13th day	—	60 drops	in 9	gallons of water.
	14th day	—	60 drops	in 9	gallons of water.
3rd Week	15th day	—	60 drops	in 8	gallons of water.
	16th day	—	60 drops	in 8	gallons of water.
	17th day	—	150 (10 c.c.)	8	gallons of water.
	18th day	—	150 (10 c.c.)	8	gallons of water.
	19th day	—	150 (10 c.c.)	8	gallons of water.
	20th day	—	150 (10 c.c.)	8	gallons of water.
	21st day	—	150 (10 c.c.)	8	gallons of water.
4th Week	22nd day	—	150 (10 c.c.)	4	gallons of water.
	23rd day	—	150 (10 c.c.)	4	gallons of water.
	24th day	—	225 (15 c.c.)	4	gallons of water.
	25th day	—	225 (15 c.c.)	4	gallons of water.
	26th day	—	450 (30 c.c.)	4	gallons of water.

Further increase in dosage was not attempted because 30 c.c. of the tincture of *Rhus tox.* in four gallons of water, an approximate dilution of 1:500, was followed by an acute generalized pruritis which lasted a week. Treatment was stopped for a few weeks and resumed with 5 c.c. in four gallons of water and then gradually increased to 10 c.c., 15 c.c., 20 c.c., 25 c.c., and 30 c.c. Once again when the dose of 30 c.c. was reached, the patient developed pruritis which was more marked on those areas of his body where the poison ivy generally developed. No further treatment was taken.

Following this course of therapy the patient exposed himself on four different occasions in four different localities, where poison ivy existed in abundance, without developing any symptoms whatsoever. With increased confidence he went through a region full of poison ivy without sleeves or stockings (something he could never think of doing formerly). The result was a small isolated vesicular lesion on one ankle which quickly disappeared with local treatment that formerly was ineffective. No further baths have been given because I am anxious to observe the duration of this apparent immunity. The patch test in different areas now shows only a very slight positive reaction to the tincture of *Rhus tox.* after twenty-four hours, and this faint reaction is hardly noticeable after thirty-six hours. This presents a striking contrast to patch tests before treatment which were marked in twelve hours and persisted for days.

COMMENT

The simplicity of this new therapeutic procedure seems to me to warrant this preliminary report in the hope that other observers with greater opportunities may determine its usefulness. Obviously, there is a real danger of initiating an attack of poison ivy by this method. This I think can be obviated by employing very weak sponge baths, increasing the dose only very cautiously and stopping the treatment at the first sign of pruritis, or dermatitis. It is hoped that recurrent attacks of *Rhus* dermatitis may be prevented by this method.

SUMMARY

1. A new method of local immunization to poison ivy is described which involves the direct application of gradually increasing doses of an extract of poison ivy by means of daily baths.

2. This procedure proved harmless and successfully prevented recurrent attacks of poison ivy in a patient in whom all other recognized methods of therapy had failed.

3. In order to obviate the danger of inducing an attack of dermatitis, the initial dilutions must be very great and the concentration must be increased very slowly and continuously.

4. It is suggested that other types of contact dermatitis may be treated by this method.

5. The permanence of the acquired local immunity is still to be determined. Further studies in this direction are being undertaken.

REFERENCES

1. Andrews, G. C.: Diseases of the Skin, New York, 1930, p. 313, W. B. Saunders Co.
2. Duncan, C. H.: New York M. J. **104**: 901, 1916.
3. Strickler, A.: J. Cutan. Dis. **36**: 327, 1918.
4. Schamberg, J. F.: J. A. M. A. **73**: 1213, 1919.
5. Clock, R. O.: Ann. Clin. Med. **4**: 591, 1926.
6. Spain, W. C., and Cooke, R. A.: J. Immunol. **13**: 93, 1927.
7. Krause, G. L., and Weidman, F.: J. A. M. A. **84**: 1996, 1925.
8. Templeton, H. J.: Arch. Dermat. & Syph. **20**: 83, 1929.

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RELATIONSHIP OF HEAT AND EFFORT SENSITIVENESS AND COLD SENSITIVENESS TO FUNCTIONAL CARDIAC DISORDERS INCLUDING ANGINA PECTORIS, TACHYCARDIA, AND VENTRICULAR EXTRASYSTOLES*

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IT HARDLY comes within the scope of this paper to review work which I have published at length on the subject of heat or effort sensitiveness or cold sensitiveness. Articles on this subject can be found in earlier numbers of this Journal this year, in the *Archives of Internal Medicine,* in the *Encyclopedia of Medicine,* and also in the *Practitioner's Library of Medicine* to be published at an early date.

Suffice it to say that I have found in studies extending over some ten years or more that practically all of the symptoms characteristic of allergy can be reproduced in certain patients by the sense of heat or by the heat produced by effort and in others by the sense of cold. The symptoms occur just as quickly as they do in a pollen case after an overdose of pollen and are just as profound. Also, they can be relieved by adrenalin in the same way that pollen reactions can be relieved. Furthermore, patients sensitive to heat and effort can be relieved by avoidance of exposure to heat and effort beyond their threshold of tolerance or by treatment with heat and effort designed to develop tolerance which enables them to lead an ordinary life of activity without reaction. Cold sensitive cases can be given tolerance for cold with even greater ease and can be transformed from a state approaching invalidism to almost normal health without any other treatment of any sort.

It is well known that certain types of angina pectoris, tachycardia, and cardiac arrhythmia are affected in a peculiar way by heat or cold or effort. I have studied this type of illness in allergy patients who are heat or cold sensitive and have found that I can produce at will, in certain cases, attacks such as angina pectoris, in other patients extreme tachycardia, and in still other cases cardiac arrhythmia by heat or effort or by cold and can relieve them immediately by the opposite application. Furthermore, I can give tolerance for heat and effort or cold to patients of the sort and relieve them completely without other treatment. I can also relieve the conditions mentioned with adrenalin.

I am convinced that in many cases of functional and organic heart disease, serious manifestations, such as extreme tachycardia (rates such as 160 to 180), angina pectoris, and cardiac arrhythmia, are precipitated

*Read before the Tenth Annual Meeting of the Association for the Study of Allergy, New Orleans, May 8 and 9, 1932.

by unbelievably small degrees of heat on the one hand or of cold on the other, and are relieved almost immediately by a sense the reverse of the one which caused the symptoms. This makes it appear clinically that the patient is neurotic. However, that is not the case. They are as consistent in their reactions to the sense of heat or effort or to cold as the patient with pollen disease is in his reactions to pollen.

I wish to describe in this paper an illustrative case in which angina pectoris which can be brought on immediately by heat or effort and relieved immediately by cold, a case of ventricular extrasystole which can be precipitated at will by cold and which can be relieved immediately by heat or effort and to refer to two cases of extreme tachycardia reported previously which can be precipitated at will by the sense of heat or effort and relieved by the sense of cold and, finally, to suggest practical therapeutic measures for their relief.

CASE 1.—*Angina Pectoris Caused by Heat or Effort and Relieved by Cold.* The patient, a married woman of forty-five years and the mother of a daughter who has hay fever, gave a history of having been subject, for five weeks, to spells characterized by a feeling of viselike constriction in the precordial region with pain radiating into both arms, into both sides of the neck, and occasionally even into the left leg. These attacks of pain were brought on four or five times daily and frequently more often, by such slight exertion as walking up a few steps or moving too rapidly or by lifting something. She occasionally had attacks during the night if she would turn over too quickly in bed.

The history was otherwise uninteresting except for a past history of typhoid.

Family history for allergy was negative except as mentioned.

The patient gave a normal physical examination. Heart and chest normal and pulse normal. Blood pressures 135.

Laboratory tests of blood and urine were negative. Stomach juice showed an achylia. Sensitization tests with more than four hundred materials gave negative or indefinite reactions. X-ray examinations of teeth and chest were negative. Basal metabolic rate was plus three.

Heat, Effort, and Cold Tests. The application of heat from a large therapeutic nitrogen lamp for periods of a few seconds would precipitate a typical attack of angina pectoris with pain radiating from the precordial region into the arms and neck. This was not associated with any noticeable change in heart or pulse. The attack could be relieved within a matter of seconds by the application of ice to the skin of the forearms. This phenomenon could be repeated at will.

The effort of stooping over six or eight times would bring on a similar attack which could be similarly relieved by the application of ice to the forearms.

It made little difference whether or not either heat or ice was applied

to the body or to the extremities distal to a tourniquet which cut off the supply of blood so long as the skin area heated or cooled was large enough and the treatment continued for an adequate length of time which, in every case, was a matter of seconds.

Attacks of anginal pain brought on by heat or effort could be relieved immediately by nitroglycerin placed under the tongue.

The patient was treated through bringing on repeated attacks by heat or effort and relieving them immediately with cold so that the patient could stand, at the end of four weeks, at least one hundred times as much heat as formerly without ill effect and could tolerate such exertion as a normal sedentary life necessitated with few attacks a week as compared with her former attacks which appeared many times daily.

It was noticed during treatment that prior exposure to cold sensitized her to the effect of heat and effort and also that ice applied suddenly to the skin which caused effort or shivering would precipitate attacks. This is the rule rather than the exception in heat sensitive cases—that is, cold increases sensitiveness to heat and overexposure to cold causes shivering and subsequently a heat reaction.

CASE 2.—*Cardiac Arrhythmia Caused by Sensitiveness to Cold.* The patient, a man of twenty-six years, had been under my care for four years for treatment for seasonal hay fever caused by sensitiveness to some of the tree pollens, grass pollens, and a large number of weed pollens. The skin tests were intensely positive for a great number of the pollens, most markedly for Bermuda grass, crab grass, Russian thistle, and the short and giant ragweed of this district. Tests for other materials were negative except for the pea and bean group of foods.

Under pollen treatment, the patient was clinically relieved and had kept his tolerance up for pollens by preseasonal treatment or by perennial treatment from the spring of 1928 to the present time.

In April, 1932, he came in with a history of having had "influenza" in the winter associated with cough, fever, nervousness, sleeplessness, and "skipping of heart beats" which had lasted until the time he consulted me. He had been forced to take hypnotics frequently since this illness started and on account of nervousness, sleeplessness, weakness, and palpitation had been compelled to quit work.

Physical examination when he first came to me in 1928 was normal throughout as were also laboratory tests of the urine and blood. Physical examination at the time he came in April was also negative except for an extrasystole which occurred regularly with every third beat of the heart.

The heart was normal in size and the sounds were normal—in fact, the only abnormality which could be found in the boy at that time was the extrasystole which proved by electrocardiogram to be ventricular.

Tests of the blood and urine again were negative. Sensitization tests were not grossly different from those obtained at a prior time except that he reacted strongly to a greater number of pollens than he had formerly.

Heat and Effort Tests and Cold Tests. Heat applied by a large lamp to the chest caused the extrasystoles to disappear completely within a period of less than one minute. Extrasystoles could be brought back as before consistently by rubbing ice on the chest or arms for less than one minute and would occur as previously, with every third heart beat.

Heat applied distal to tourniquets around the arm would cause a similar disappearance of the extrasystoles. These would reappear after application of cold to the forearms also distal to tourniquets. The effort

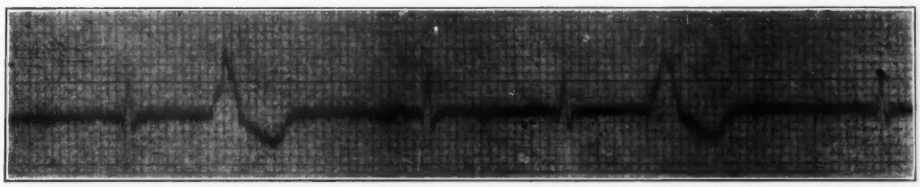

Fig. 1.—Electrocardiograph illustrating cardiac arrhythmia under the usual conditions of living.

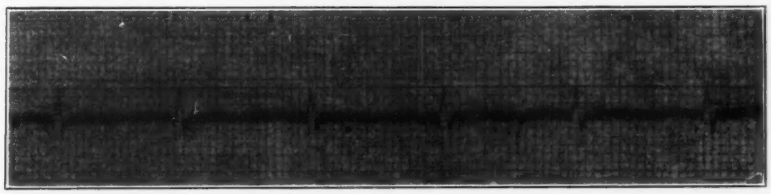

Fig. 2.—Electrocardiograph illustrating change in cardiac rhythm which could be consistently produced by heat applied to the chest, by heat applied to the arm distal to a tourniquet which stopped the circulation of blood, or by the heat generated by physical effort.

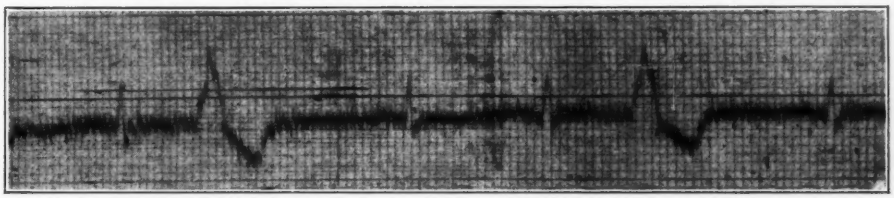

Fig. 3.—Electrocardiograph showing recurrence of arrhythmia. The extrasystoles would consistently reappear if patient's arms were rubbed with ice after the arrhythmia had been relieved by the effect of heat or effort. Through the effect of treatment daily with heat and cold, as described in the text, the patient consistently showed the normal rhythm illustration in the electrocardiograph of Fig. 2. At such times the arrhythmia could be brought on at will by the application of ice to the arms or body and could be again relieved through the effect of heat or effort.

of bending over and straightening up a number of times would likewise cause a disappearance of the extrasystoles.

An adrenalin test made at the height of his illness proved to stop the extrasystole if administered to the point of causing slight tremor of the hands.

The above tests were made repeatedly and proved by electric cardiograms and always gave the same result.

The patient was treated through frequent application of heat and cold

and with graduated exercise, the extrasystoles being stopped when they reappeared by the effect of heat and effort. After a period of two weeks, one would have to feel the pulse for a minute or so before even one abnormal beat could be found. Usually, there was no arrhythmia present at all. However, extrasystoles could be made to appear by the application of cold. The patient during this month had gained in weight and strength and resumed his occupation. His nervousness disappeared and he stopped taking hypnotics.

Two Cases Illustrating Tachycardia amounting to a little less than a doubling of the heart rate which could be brought on by similarly small amounts of heat or effort and relieved by cold and which were permanently relieved by an increasing of their tolerance for heat and effort are described in a previous paper. [1]

DISCUSSION

Reactions such as these above cited can be explained, I believe, very often by the finding of an injury at some point in the heat regulating mechanism. This is often demonstrable. Frequently in patients in whom no abnormality whatever can be found, we do find a history of a febrile disease antedating the onset of symptoms, especially such illnesses as the infectious exanthema, chorea, rheumatic fever, pneumonia, and typhoid fever.

The heat regulating mechanism includes for its normal working several important structures—the skin and respiratory apparatus as cooling membranes controlled largely by the respiratory center, the circulating fluids controlled by the heart and vessels, and vasomotor center, a thermostatic mechanism in the midbrain, the sense organs for the perception of heat and cold, and the endocrines, especially the thyroid and adrenal which have a profound effect upon metabolic rate and heat regulation. Also should be included voluntary actions of the individual made for the purpose of heating or cooling himself.

When the heat regulating mechanism is injured at one or more points, the defect is no doubt compensated for by increased activity of the apparatus at some other point. Frequently the compensating reaction is exaggerated or perverted and sometimes does as much harm as good. For example, I observed a boy who after an attack of measles lost the faculty for sweating. He was thereafter short of breath on exertion. The respiratory apparatus eventually compensated, in a way, for the falling down of the skin in its function of body cooling. It was primarily useful but often after extremes of exertion, caused him to have asthma. Similar compensations which are not always constructive, may occur in other internal organs and give rise to disorders of one kind or another in one of several localities and apparently in some cases may cause irregularities in the normal behavior of the heart.

CONCLUSIONS

In this paper I have mentioned three types of cardiac disorder—extrasystoles, tachycardia, and angina pectoris, which occurred in individuals who gave normal physical examinations.

The above abnormalities could be brought on consistently by the effect of the sense of heat or by effort in three cases and by the sense of cold in the other.

The abnormalities produced could be relieved by applying an agent the reverse of the one which caused the abnormal reactions.

The conditions were benefited by treatment with the agent responsible for the illness.

The disorders are believed to be due to disease in the heat regulating mechanism and in these cases by abnormal responses to the sense of heat or the sense of cold or by the heat produced by physical or mental effort.

The electrocardiograms used in this study were made and interpreted by Dr. Graham Asher.

REFERENCE

1. Duke, W. W.: Heat and Effort Sensitiveness. Cold Sensitiveness, Arch. Int. Med. **45**: 206, 1930.

(For discussion, see page 66.)

SOME OBSERVATIONS ON THE VALUE OF INTRATRACHEAL INJECTIONS OF IODIZED OIL FOR BRONCHIAL ASTHMA*

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ABOUT seven years ago, while using iodized oil for diagnostic purposes, my attention was directed to the improvement that often followed the injection of iodized oil into the lungs of certain patients with bronchial asthma. This was a suggestion that seemed to be worth further consideration, and I began a study of the problem in order to determine whether the intratracheal injection of iodized oil was of any value in the treatment of this disorder.

These observations are based on a study of 60 cases drawn from private practice and from the wards and dispensary of the Western Pennsylvania Hospital, Pittsburgh. They were unselected as to etiologic factors, duration of the condition, or age, with the one exception that children under twelve years of age, owing to the technical difficulties of injecting the oil, were excluded until positive evidence of the value of this method of treatment was fully established. Most of the patients were of the chronic type and had received the various treatments for this condition without results.

There is only one patient in the group in whom the duration of asthma was less than four years. In all others the condition had existed from four to forty-eight years. In many of the cases the asthma had existed from infancy or early childhood. About half the number of this group were susceptible to foreign proteins; in the other half, the excitant was peripheral, psychic, or due to infection of the respiratory system. Influenza took the lead among the various infections of the respiratory system. In many of the patients this condition was accompanied by chronic bronchitis, hay fever, emphysema, or myocardial changes of years' duration. Dyspnea due to the emphysema was as distressing to the patient as were the asthmatic paroxysms.

Response to the treatment with iodized oil varied widely, and in certain obstinate cases a changed chemical composition has seemed indicated, and has been attended with improved results clinically. In certain types of cases the response has been prompt; but in others, tardy, months being required to bring relief of definite character.

That the administration of the oil should be cautious is indicated by the fact that in some cases the first injection precipitated an immediate attack, which, however, was usually followed by definite improvement. In the others, the attacks decreased in frequency and severity after the

*Preliminary report.

first injection. As the treatments continued, the attacks became less frequent and severe and faded into slight attacks of shortness of breath, and then into attacks, possibly nervous, without shortness of breath. As a rule, the younger the patient and the shorter the duration of the condition, the more prompt the response.

When the excitant was a foreign protein, the response was usually very prompt. Where the attacks were preceded or accompanied by hay fever, the vasosecretory symptoms diminished rapidly after the first few injections of the oil and usually disappeared before the asthmatic paroxysms. A rapid decrease in the clinical hypersensitiveness to known excitants was observed in every case. When the cause could be traced to a respiratory infection, especially influenza, the response was usually slow and difficult to obtain.

In every case where a bronchitis was present, the cough was relieved with noteworthy rapidity. In many cases where the patient had coughed almost incessantly for years, the first few installations of oil yielded prompt relief. Coincident with this there was a marked gain in the patient's general health, presumably due to freedom from the attacks.

The amount of oil, the frequency of the injections, and the area of the lung injected varied with each patient. It will be seen by this that each case must be treated individually, and much of the success depends upon one's ability to interpret conditions properly and to vary the treatment accordingly. Although the lung reacts favorably to the oil in most instances, there are certain untoward reactions characterized by pain, pressure, and temperature, which require judicious and careful handling. But generally speaking, the contraindications are few, especially when one considers the highly favorable results that our experience to date presages for the treatment.

The result obtained in all of the cases is most gratifying. Twenty-four out of the 60 cases have been entirely relieved of all symptoms for from one to five and one-half years. The remaining 36 have been under treatment only from three to twelve months, but all of them have, in that time, been appreciably relieved. More patients, of course, must be observed for longer periods before final judgment may be passed on the merits of this treatment for asthma. However, in regard to those so far treated, in which none has failed to respond, it may be said that the relief obtained exceeds that from any other methods employed with them.

Although much must be learned by further study, the observations to date reveal several interesting points. The obstructions in the lumen of the bronchial tubes, which are no doubt caused by coagulated mucus forming casts which partially or completely plug the tubes, existed both during and between the attacks of asthma and disappeared after sufficient contact with the iodized oil. The casts were often found in the sputum after the injections. These obstructions are at least quasi per-

manent; for they can be observed during the attack of asthma and in the intervals between attacks and, therefore, would not appear to be due primarily to a spasm of the circular fibers of the bronchial muscles, whose effect is more transitory. It was necessary to overcome these obstructions, which was a major objective of the treatment. As one might expect, a priori, its attainment is by no means always a simple matter, but details are reserved for a more complete presentation than this is intended to be. It seems likely that this condition would make for a constant interference with free drainage of the bronchial tubes beyond the point of obstruction resulting in imperfect ventilation of the lung.

There seemed to be a direct relation between the frequency and the severity of the attacks and the number of plugged tubes. But when their patency was finally established, relief from the asthmatic paroxysms was prompt and definite.

Jackson[1] has called attention to the part hardened secretions have played in the obstruction of the bronchial tubes. He says "secretions when viscid or hardened into crusts have, in many cases, completely corked a bronchus of normal size lumen and produced a check valve obstruction. In many cases of asthma the air hunger seems to be due to pumping out of the air from both lungs. Bronchoscopic removal of the secretions that were acting as check valves almost always cured the air hunger."

This position is supported by a recent statement of Steinberg[2] who made a study of roentgenograms taken after the injection of iodized oil in the asthmatic attack and during the interval, in addition to correlating these observations with postmortem findings of patients dying from allergic asthma. He concludes from his study that the paroxysm is due to occlusion of the tubes with mucus, which is the result of hyperactivity of the bronchial mucous glands.

It is clearly recognized, of course, that the number and scope of these cases must be extended before claims of a formal nature could be made in behalf of this method in treatment of asthma and associated conditions. It is highly desirable too that further inquiries be made into the modus operandi of the oil aside from the mechanical effect of promoting free drainage.

It is obvious that the clinical effects raise certain questions of interest, such, for example, as the prolonged freedom from symptoms and their relation to skin sensitivity to various specific asthmatic incitants. Such problems are under survey by the Hospital's Institute of Pathology, particularly in their relations to the clinical results obtained.

CONCLUSIONS

1. Roentgenograms of lungs of asthmatic patients after intratracheal injections of iodized oil reveal plugging of many medium and small sized bronchi.

2. This obstruction of the bronchi disappears after injections of iodized oil.

3. Patients injected intratracheally with iodized oil lose their hypersensitive response to known excitants.

4. On the supposition that there might be some relation between the plugging of the smaller bronchi with mucus and the asthmatic syndrome, a series of 60 patients has been treated by intratracheal injections of iodized oil. The 24 completed cases have been satisfactorily relieved. The remainder now under treatment have shown great improvement.

REFERENCES

1. Jackson, Chevelier: J. A. M. A. **95**: 639, 1930.
2. Steinberg, B.: J. ALLERGY **3**: 139, 1932.

SUMMARY OF RESULTS OF TEN YEARS' HAY FEVER TREATMENT*

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IN SUMMARY of ten years of hay fever treatment, when testing methods, extraction technic and treatment are undergoing continuous change, the main benefit, if any, of such a paper is to indicate changes. The greatest help comes, not from success, but from failure and error.

In Colorado the hay fever problem is different from that of almost any other section. Here the dust storms in February and March produce hay fever symptoms from the last year's pollen. The time of pollination varies with each 1000 feet of elevation. A wet spring will give the grass such a start that the Russian thistle will be almost completely choked out. In a dry spring the grass except in the lawns never starts to grow. Instead of a few pollens there are seventeen distinct varieties of pollens which cause hay fever. August finds eight different pollens in the air.

The hay fever season starts about the middle of March with the elm trees. Within a week, the maple trees are pollinating. These two trees pollinate for about two weeks, and then there is a slight lull; and the poplar trees start. These are scarcely well started when the cottonwood trees begin and carry over into May. These four trees make up the majority of the trees in the city and in the town. As May opens, the dandelions in every lawn start pollinating and continue well into the summer. June sees June grass, which makes up practically all the lawns, starting to pollinate. The first of July, Russian thistle to which 79 per cent of patients react starts pollinating and continues until September. Pigweed and lamb's-quarters join thistle about the tenth of the month. The middle of the same month, the sages begin, and as there are roughly six varieties, they continue according to altitude and moisture until October. The first of August, kochia, otherwise known as burning bush, throws large quantities of pollen into the air. By the fifteenth, if the season is warm, ragweed begins pollinating, followed closely by marsh elder. Thus in August there is pollen in the air from the following weeds (the percentages of patients reacting to each is given): thistle 79.7 per cent; pigweed 64.7 per cent; lamb's-quarters 64.7 per cent; sages 52.4 per cent; kochia 64.5 per cent; ragweed 52.9 per cent; marsh elder 35.9 per cent; sunflower 17.8 per cent. Hence the problem of giving 100 per cent relief from symptoms is very difficult as many patients are sensitive to so many pollens. They average 5.9 per cent separate pollens to the patient. Ex-

*Read by title before the Eighth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, April 30, 1932.

perience has shown that for complete relief, the patient must be desensitized to every pollen to which he reacts and contacts. The problem is further made more difficult by a very dry climate.

All patients have been tested by the scratch method. The solutions used have been 1 per cent extracts with glycerin 66.6 per cent and saturated salt solution 33.3 per cent—and diluted with Coca's solution. The pollen is usually cleaned by overlaying carbon tetrachloride with ether in a separatory funnel. The pollen is stirred into the ether. The carbon tetrachloride and dirt are then drawn off below. The pollen in ether is run into a sterile filter paper.

By autoclaving all glassware and filter paper, the pollen can be removed from the glycerin extract by simple filtration. The filtrate is protected from the air currents as much as possible. Occasionally the filtrate is contaminated but usually it is sterile. If contaminated, it can then be put through a Berkefeld filter or a new solution prepared.

In view of Brown's recent paper[1] it is interesting to note that no patient has received a higher dose than one minimum of 1:100 solution. This probably explains the none too glowing results. However, it does not explain the patients who receive 100 per cent relief from 1 dose of a 1:10,000 dilution. There were only 2 such patients, but they do exist.

Severe general reactions, in my opinion, are not so much a question of dosage as a question of individual susceptibility. Last year a patient was refused treatment and the mountains were suggested as an easier relief, because for two years she had experienced a severe general reaction when taking the 1:1000 solution, although no other patient had been troubled. Severe systemic reactions occur usually in 1 per cent of the cases. Last year, there were none. Undoubtedly some general reactions are due to getting the solution directly into the small vein.

A few years ago 100 patients who had taken treatment throughout the season were sent a questionnaire in regard to the results of treatment. They averaged 72 per cent relief. This year all patients who had ever been under treatment for the past ten years received a questionnaire. As a large number of patients seemed to obtain permanent relief after three years' treatment, the questionnaire requested the percentage relief obtained in the first, second and third year of treatment; and in addition, if asthma were present, was it cured by the treatment?

Results are interesting because they represent not an allergist's results, where a case is under direct supervision, but the result where the treatment is given by medical men, surgeons or nurses scattered over several states, usually not interested and often very skeptical of the value of such treatment.

The questionnaire was sent to 600 patients, 231 replies were received which could be used. These patients averaged on their own figures, 59.4 per cent relief the first year, 66 per cent relief the second year, and 71.7 per cent relief the third year. The first year 10 per cent received

100 per cent relief; the second year 7.8 per cent received 100 per cent relief; the third year 4.7 per cent received 100 per cent relief. Those receiving 100 per cent relief in any one year were usually advised to go without treatment the succeeding year. This explains the decreasing number receiving 100 per cent relief. Apparently, a patient thus relieved may have fairly comfortable summers for two or more years without treatment. Thirty-four and two-tenths per cent had asthma, and averaged 72.3 per cent relief. Of these 33 per cent obtained 100 per cent relief from asthma.

Among these 600 cases there have been 3 cases of pollen eczema. One had severe eczema and practically no hay fever. The other two had severe hay fever and very mild eczema. The severe eczema was sensitive to marsh elder (*Iva xanthafolia*). The eczema of one of the others was caused by dandelion and the third by ragweed. All these received complete relief from treatment with the 1 per cent pollen extract hay fever solutions. The patient with the severe case cannot take a dose higher than 1:5000 dilution without producing small areas of eczema, and although he has been tested with pollen oil, and had a severe reaction, he is afraid to take the treatment because of his extreme sensitization.

In conclusion the best that can be said is that the results obtained under the present methods of treatment are not highly satisfactory; that first-class results may be obtained only by the complete cooperation between patient and the allergist; that pollen asthma is more easily relieved than pollen hay fever; and that pollen eczema is present in about 0.1 of 1 per cent of hay fever patients and responds to the usual hay fever treatments.

REFERENCE

1. Brown, G. T.: J. ALLERGY **3**: 180, 1932.

932 REPUBLIC BLDG.

UNUSUAL CASES OF MIGRAINE WITH SPECIAL REFERENCE TO TREATMENT*

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DURING the past five years migraine has been studied as never before. It may be defined as a disease characterized by paroxysmal headache which may be facial, ophthalmic, hemicranial or cranial in distribution, nausea, vomiting and quite often abdominal pain, and preceded as a rule by an aura. It is hereditary in origin, interchangeable in the linkage with other allergic diseases and follows the Mendelian law.

During the past three years I have studied 43 cases of true migraine from both the allergic and the general medical points of view. In this series of cases 28 were females and 15 were males. The ages varied from eight to sixty-five years. All were of the white race. The family history for allergic disease was positive in 30 cases, or about 70 per cent. It is quite probable, however, that a negative family history of allergy implies only ignorance of the family afflictions.

Another factor militating against a positive family history in all cases is that a parent may be able to transmit the tendency to the offspring, and at the same time may show no evidence of the disease. In this event, naturally, the family history would be negative. I believe that allergic disease is probably 100 per cent hereditary.

From a pathologic standpoint we have very little to go on except theory. One of my patients has had a decompression of the right temporal region for relief of headaches. This was done about ten years ago. When the headache occurs now, there is a definite bulging in this area with a definite vascular pulsation. This indicates to me that in migraine there is a vasodilation or swelling in the brain, meninges, or both. I doubt whether a purely local urticaria of the meninges could cause such a marked bulging as this patient has, unless it occurred just at the site of the operation. It is reasonable to assume, however, that a blocking in the ventricles could occur, producing distention, which in turn would cause the aforementioned bulging and pulsation due to congestion with resulting edema and vascular dilation.

From a practical, clinical and therapeutic standpoint migraine may be classified as, allergic, endocrine, combined, miscellaneous (due to all other causes).

The symptoms are usually referable to the head, eyes, nose, ears, face and gastrointestinal tract. Any combination of symptoms may exist and they vary in different individuals. In the true allergic migraine

*Read before the Tenth Annual Meeting of the Association for the Study of Allergy, New Orleans, La., May 9 and 10, 1932.

nasal symptoms may or may not be present. After the headache subsides the nasal symptoms and signs usually subside. Often in these patients the first sign of an oncoming headache is nasal congestion.

In migraine of the endocrine type, symptoms occur referable to the thyroid gland (usually a deficiency), to the ovary and pituitary. Quite often we see women who tire easily after the least exertion, are irritable, very nervous, suffer with palpitation and attacks of tachycardia. They have rather severe headaches, migrainous in character, their metabolic rates are low, menstrual disturbances are common, or the menopause may have been established either in the natural course of life or by artificial means.

As a rule the allergic type is most common, but quite often one sees the combined type. In this type, symptoms and physical findings are apparent, which lead one to suspect that allergic disease exists as well as an imbalance in the endocrine system. This becomes evident after a complete history has been taken and a thorough physical examination has been made, which should include all laboratory aids. In this series of 43 cases, 12 or 28 per cent were of this type.

Under the miscellaneous type are included migrainous headaches, due to other causes or in combination other than those previously mentioned. I have had under observation 20 such cases which I have not included in this study.

TREATMENT

The first step in the successful management of this disease is to make a correct diagnosis, not only as to the disease but as to its type, or combination of types. In the literature great stress has been laid on specific hypersensitiveness to foods, but other factors such as animal hairs and danders, pollens, foci of infection, fatigue states, etc., are merely mentioned as secondary factors, with the statement that they should be removed as far as possible.

In this series of cases there have been 14 in which my findings have been rather unusual. Skin tests to foods were positive in 9, or 64 per cent. They were considered as major factors in each instance where found definitely positive. However, after elimination very little, if any, relief occurred from their withdrawal from the diet of these particular sufferers. All inhalants, pollens, etc., had been eliminated, as well as all other factors so far as could be determined. As a last resort I decided to try treatment with specific extracts and vaccines. The extracts were not of foods but of pollens, animal hair and danders, orris root, and in two instances bacterial vaccines. Practical relief was obtained in each of these 9 cases and has been maintained since this plan of treatment was instituted. All foods were allowed in the dietary, even though they gave definite positive skin reactions. No ill effects have been noted up to this time.

In 12 cases, even with the administration of specific extracts, relief while practical was not as much as I thought it should be, therefore, metabolic studies were made and thyroid dysfunction noted if present. If a history of menstrual disorders, pelvic operations, sexual dysfunction, etc., was obtained with definite clinical evidence, ovarian dysfunction was assumed to be present. A greater percentage of relief was afforded these patients by the judicious use of appropriate glandular extracts in addition to allergic therapy.

Chronic duodenal stasis is often associated with allergic migraine, as well as the combined endocrine types. In these cases, on x-ray examination, a churning action can be seen in the duodenum, similar to that often described in gall bladder diseases, or obstruction in the upper gastrointestinal tract. When this condition exists, upper intestinal cleansing is indicated and produces its share in the percentage of relief afforded the patient.

In one case, "Flytox," as well as other insect powders and liquids, was found to be the sole cause of the migraine. Complete relief was obtained by change of occupation and elimination.

All cases of migraine cannot be treated as a group. Each case must be treated as an individual. Foods are the causative agents in a great many cases, undoubtedly the majority, but it is well to remember that foods, even though positive, play a minor rôle in the production of migraine in quite a few cases.

Absorption of inhalants from the upper respiratory tract is quite rapid. It is not unreasonable to assume that when these inhalants are absorbed in sufficient quantity they cause allergic imbalance and produce allergic phenomena, in one form or another. Occasionally one finds a case in which an inhalant such as grass pollen, or orris root produces an allergic phenomenon, atypical in type for that specific substance. In one of my cases typical migraine was produced by a sensitivity to grass, feathers and orris root. Treatment with grass extract has relieved this patient completely. Orris root and feathers were eliminated.

The cases I am about to report are not those of hay fever with secondary headache, but are cases of true migraine in which the nasal and respiratory symptoms were of a local nature, and the headache due to absorption of the inhalants and their resultant general effects.

CASE REPORTS

CASE 1.—Doctor V. J. D., aged thirty-five years, male, white, surgeon. *Family history* positive for allergy. *Past history*—several sinus operations.

Present illness: For twenty years patient has had periodic headaches occurring in the beginning about every month, then each week, and at present awakens practically every morning with blinding headache. He is incapacitated and cannot operate. Aura precedes the headache. The

day before he feels fine and is extremely hungry. The headache begins over both eyes, gradually covering the entire head. He eats highly seasoned, Italian foods. He hunts fall and winter, and is quite fond of dogs.

Positive skin tests: Chicken, duck, goose, quail, turkey, canary bird feathers, dog hair, cat hair, sheep's wool and horse dander all gave 4 plus reactions. Thirty-four foods gave from 2 plus to 4 plus reactions.

Treatment: All foods found positive were eliminated from diet. All animal hair and danders were eliminated, and patient was observed for one month on the above régime. He said he was better, but there was a great deal of room for improvement. Treatment with dust and feather extract was started at this time. He was placed on a full diet after the first month with no ill effects. Every spring in May, and fall in October terrific headaches occurred with nausea and vomiting. He kept his clothes in a cedar chest and with the change of season changed his clothes. Evidently, this was the cause of these headaches, as elimination of the cedar chest has relieved him of headaches at this time.

After studying this case carefully we found his metabolism was normal, spinal fluid negative, blood sugar 100 mg. per 100 c.c., blood urea elevated to 18 mg. per 100 c.c. Urine was highly colored, but otherwise negative. Definite pyloric spasm was found with peculiar peristalsis in the duodenum. Rest of examinations of gastrointestinal tract and gall bladder were negative. Blood count was normal, except for an eosinophilia of 5 per cent.

With the foregoing findings we allowed him a full diet, preceded by tincture of belladonna. Bile salts were ordered after each meal. Animal extract injections were continued. His recovery has been phenomenal. He is doing his work and says he feels better than he ever has as long as he can remember.

CASE 2.—G. A., aged twenty-two years, female, white, registered nurse. *Family history* positive for allergy. *Past history:* Decompression operation ten years ago for relief of headaches. Several sinus operations.

Present illness: Headaches have occurred as long as she can remember at irregular intervals. They start as a dull pain over right eye, radiate backward and go over entire head. Duration of headache is from twenty-four hours to several days. For the past year she has had a cough, productive in type and occurring in the morning on arising.

Positive Skin Reactions: Dust, wheat, milk, cheese, barley, corn, celery, lettuce, parsnip, codfish, lobster, crab, oyster, scallop, shrimp, almond, pecan, squash, cabbage, cantaloupe, cocoanut, ginger, grapefruit, chicken feathers, duck feathers, goose feathers.

Treatment: All foods were eliminated that were found positive. This gave some relief. Extract of dust and feathers gave more relief. An autogenous vaccine was made from her bronchial secretion. This vac-

cine was added to her therapy and since then she has had practical relief. When wheat is taken a headache develops, in spite of the other treatment. If the other treatment is left off, the headaches return.

CASE 3.—R. O. J., aged fifty years, white, female, housewife. *Family history:* Gave negative allergic history, but I am treating her first cousin for hay fever and asthma. *Past history:* Thyroidectomy twice.

Present illness: For years patient has been having periodic sick headaches. She thinks that getting very tired or upset brings them on. Menopause since May, 1920. Face powder makes her sneeze and her nose run, the eyes burn and itch, but not unless the powder gets into her nose, so she holds her nose when she powders her face.

Skin tests: Grass 4 plus, feathers 4 plus, orris root 4 plus. All foods gave negative reactions.

Treatment: Orris root-free face powder was given her, as well as orris root-free accessories. Feathers were removed from her home. She was treated with grass extract and orris root extract. She has been under observation for past six months and says that she has been well.

CASE 4.—J. C., aged thirty-three years, female, white, housewife. *Family history* positive for allergy. *Past history:* Abdominal operation seven years ago—hysterectomy. Left antrum drained two years ago.

Present illness: Four years ago the patient had sneezing spells on arising in the morning. This persisted for two years. At the present time she has a postnasal drip. There is crust formation in back of her nose at night. Her ears itch a great deal. Intermittent pain in right upper abdomen. For past two years at irregular intervals has had severe, blinding headaches with nausea and vomiting. She is awakened from her sleep by headaches. The headache usually passes off in from eight to twelve hours. At times when she goes to bed she gets short of breath and wheezes considerably.

Skin tests: Chicken feathers 4 plus, goose feathers 2 plus, dog hair 2 plus, duck feathers 2 plus, milk 3 plus.

Metabolic rate—minus 21; blood urea 21 mg. per 100 c.c. blood in the morning after attack; the following morning 15 mg. per 100 c.c. blood. Blood pressure 120/80. Urine was negative.

Treatment: Animal hair and dander were eliminated. She was treated with dust and feather extract. Thyroid and ovarian extract added to the therapy. Milk was eliminated in beginning of the treatment but she can now take milk without producing a headache. She has apparently been relieved and has been under observation for the past two years.

CASE 5.—M. B., aged forty-three years, white, female, bookkeeper in market. *Family history* positive for allergy. *Past history:* Nothing of importance.

Present illness: For the past five years in the spring and sum-

mer, she has intermittent headaches about every week or ten days. Cannot attribute them to anything she does. She gets very hungry before onset. Urine gets very dark. About two hours later headache starts over forehead, gradually covers the head and neck. They always start while she is at work and she has to go home. She vomits and at times has cramplike pain in her abdomen.

Skin tests: Pyrethum—4 plus. Patch test with Flytox—marked local irritation with large wheal surrounded by papules persisting for one week after patch was removed.

Treatment: Change of occupation, which cured the patient.

CASE 6.—D. B., aged eighteen years, white, female, college student. *Family history* positive for allergy. *Past history:* Tonsils and adenoids removed ten years ago.

Present illness: The patient has pain over left eye, gradually radiating over the left side of her head. It comes on gradually and lasts about twelve hours. Nausea and vomiting begin with the onset of the pain. During this time the least noise almost causes her to have a convulsion. She also notices that before the headache begins she thinks there are bad odors in her room or on her person. She has had a breaking out on her arm every winter for past three years. She has also had frequent colds.

Skin tests: Foods, animal hair and danders, pollens and other inhalants all negative. A culture was obtained from her nasal secretion. It was transferred to media containing the patient's blood. The growth showed *Staphylococcus aureus* and Friedlander's bacillus. Skin test with these bacterial allergens intradermal gave a 4 plus reaction. She was treated with vaccines very cautiously over a period of six months. Her headaches gradually began to lessen in severity, and the interval between headaches became longer, until at present she is rarely bothered.

CONCLUSIONS

1. Cases of migraine cannot be treated as a group, but must be treated as individuals.

2. True allergic migraine is probably hereditary in 100 per cent of cases.

3. Migraine has been classified from a general medical viewpoint.

4. Foods are of paramount importance in the majority of cases. In some cases positive skin reactions may be obtained, but elimination of these specific foods affords the patient no relief.

5. Inhalants, such as animal hair and danders, pollen, orris root, insect powder, etc., are the main factors in many cases.

6. Elimination of inhalants alone does not always procure relief. Treatment with specific extracts is necessary in some of these cases.

7. A combination of allergic and endocrine migraine is quite common. Combined therapy is necessary for relief.

(For discussion, see page 76.)

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

TENTH ANNUAL MEETING, NEW ORLEANS, LA., MAY 8 AND 9, 1932

(CONTINUED)

Clinical Experiences With Synthetic Ephedrine. R. A. KERN AND H. P. SCHENCK, PHILADELPHIA, PA. (For original article, see page 9.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—Synthetic ephedrines were brought on because of necessity, as Dr. Kern stated, because of the lack of ability to get a sufficient quantity at one time; however, there is ample supply now. At that time we became interested in the subject because of our inability to get ephedrine.

Dr. Alles, working with us, felt that it was possible to synthesize a product that was similar to and would act like ephedrine. He went to work on the subject and we reported in either 1925 or 1926, I do not remember which, the first clinical study and chemical report on a substance called phenolethenolamine, which was published in the *Journal of the American Medical Association,* and the Council of Pharmacy investigated it and discussed it editorially.

This drug has never been put on the market, nor has it been commercialized.

The drug ephetonin I know nothing about, but I should like to know what the chemical name for it is. All the synthetic work is being continued on the phenolethenolamine substances. Since then Dr. Alles had continued research on this subject and has now isolated some 34 amines. About 16 have never been heretofore described, and have given very interesting pharmacologic pictures.

At present Dr. Alles is working on this subject in conjunction with Dr. Leake, and we have produced, by changing the hook-up on the benzine ring, various actions that are really very interesting.

Getting back to the clinical side of this story, these products in our experience, first ephedrine, has rarely if ever stopped an attack once it was on. Our experience has been that it acts as a preventive or prophylactic or abortive if we know when the patient is going to have an attack, and we find that once we have stopped an attack, if we give the patient ephedrine, regardless of the dosage, that does not seem to be the factor that prevents the attack. On those people we are using quarter grains instead of three-quarters of a grain, and we find the results are equally as good. We give it before the anticipated onset of an attack.

Lately we have found that ephedrine is more irritating. I do not know whether it is the opposite of Dr. Kern's finding; that the synthetic ephedrine is less irritating. It does shrink the mucosa over a longer period of time, causing no blanching of the tissue.

We find that the untoward symptoms are practically nil, that with the ephedrine the symptoms classified by Dr. Kern were evident. In fact, about two years ago, before this Society, I reported three cases of urinary retention in which prostatectomy was done. I have never seen urinary retention in the female. I have seen, not infrequently, the retentions in males, and I believe that patients past the age of fifty years in the male sex are definite contraindication for continuous and promiscuous use of ephedrine. The acute attacks I have never seen controlled by ephedrine.

Another thing I want to bring out is a point on which I do not agree with Dr. Kern, and that is the oral administration of the ephedrines. I have never seen any of the preparations that will work by mouth, including the one we prepared ourselves. Their use is limited chiefly to the local application, and by mouth the only one that has any real value is the real, original ephedrine.

The question of blood pressures is rather interesting in that we found that the synthetic ephedrine does bring up the blood pressure, as pictured by Dr. Kern, and that all of the preparations including sympatol or synephrin, and some that are being prepared by Sharp and Dohme, do exactly the same thing. They do not increase the blood pressure as anticipated.

We have found in one of the preparations that Alles has prepared, that we can raise blood pressure with one that is known as the isopropyl preparation of phenolethenolamine or isopropylamine. That will increase the blood pressure for twelve to twenty hours, but it has toxic effects and does not warrant its use at this time.

I have never seen any one acquire a habit from ephedrine.

Dermatitis was reported by Alles last year or the year before, and he also evidenced the patch reactions.

I think that Dr. Kern's paper is very timely because of the attempt at this time on the part of many of the chemical houses to force the synthetic preparations down our throat. I think that the synthetic preparations at this time, in so far as we have been able to study them, and we have had them all for comparative studies with the preparations that Dr. Alles is studying, have given no evidence of having any value as far as the oral administration of these products is concerned.

DR. W. W. DUKE, KANSAS CITY, MO.—In my earlier experience with ephedrine, I used it in capsule form and obtained disagreeable constitutional reactions so frequently that I dispensed with the use of the drug on this account in the majority of my patients. Through using it in liquid form so that the dose could be more accurately controlled and adjusted to the patient, I obtained much better results. Also, through its subcutaneous use I have been able to control the dosage much better through mixing ephedrine with a trace of adrenalin, the purpose of the adrenalin being to constrict the vessels and retard the rate of absorption of ephedrine. Through this means, I have been able to use ephedrine successfully in a very much larger proportion of cases.

The fact is that I use ephedrine, adrenalin, and the tourniquet as described in a previous communication with a great many hypodermic injections, such as insulin, typhoid, vaccine, tuberculin, etc., and have slowed down and equalized the rate of absorption of the injected material to such an extent that reactions due to too rapid a rate of dissemination of the material from site of inoculation have practically been eliminated, and it enables me to use much larger doses of pollen, tuberculin, vaccine, insulin, or other materials without disagreeable constitutional effects.

DR. A. H. W. CAULFEILD, TORONTO.—I think the charts Dr. Kern has given us are very interesting, and I should like to ask him, with Dr. Piness, if he used more than one synthetic drug. In the charts he has given us, certain patients are benefited from one and others from another. Roughly speaking, during the last few years I suppose I have used four or five different synthetic preparations including one Dr. Piness has been good enough to send me, and it seemed valuable enough to keep three or four preparations on hand, as one patient would experience more benefit from one preparation than another.

In the case of urinary reactions, in one instance at least, where there were excellent but temporary effects, there were very bad final effects because of the urinary retention. In this case I got no such reaction if I gave it intratracheally. Most people have thought I used a bronchoscope, but we do not use this that way but drop it down over the glottis—a simple procedure.

I think it is hopeless to give it during an attack. You have to tell the patient to try to find out when he will have an attack, i. e., notice his prodromal symptoms, and take it ahead of time.

One odd feature to me is that the blood pressure always goes up if it is given subcutaneously. Even in such cases no effect on blood pressure follows when it is given by mouth.

DR. HARRY L. HUBER, CHICAGO, ILL.—In the patients made worse by the use of ephedrine, was there any relationship to blood pressure? Did they have blood pressures above normal? I have had a few patients with blood pressures above normal who did not tolerate it as well as others.

DR. RAY M. BALYEAT, OKLAHOMA CITY.—I should like to ask Dr. Kern about constipation. I do not remember that he mentioned that untoward symptom in the use of the synthetic product. The first patient to whom I ever gave ephedrine happened to be back in 1924 before the product was put on the market. We were advised by the Peking Union Medical College to give 150 mg. at a dose and repeat if necessary. This I did. The man to whom the product was given was a lumberman, and I gave him the first dose in our office and he went back to his office. He later called me and told me that his hair was standing on end. It interested me very much. He came over and I found he was truthful in his statement. This tingling symptom of the hair I have observed a good many times.

This same patient reported that the next morning he had no desire to pass urine and had difficulty in bowel movement. I soon learned that 150 mg. a day was too heavy for American people, that much smaller doses would have to be used, as we ran into untoward symptoms. This size dose is probably all right for the Chinese. I wrote Eli Lilly & Company and suggested then that they advise the medical public about the untoward symptoms. I reviewed the vegetative nervous system of the bladder, and it appeared to me from the action of ephedrine that it should cause a lack of desire to pass urine, and also have a tendency to produce constipation. We have seen a number of patients suffering with bladder retention due to the use of ephedrine.

Up to the present time we have used no synthetic products. I recently received a letter from Stearns telling me it was in answer to an article we had in the *Journal of the American Medical Association* concerning urinary retention due to the use of ephedrine. They pointed out that their product would not cause such symptoms.

I have been very much interested in mentioning the fact of urinary retention to the urologists, due to the use of ephedrine, to note that there are probably but very few of the urologists who realize that ephedrine can produce urinary retention. A urologist recently wrote me saying he had seen the article which I mentioned, and he at once inquired more carefully into the history of a patient whom he had to catheterize daily, concerning the use of ephedrine, and found that the man was using fairly large quantities of ephedrine daily. On ceasing to use the ephedrine the bladder retention, the cause of which he had not been able to determine, was relieved.

DR. MILTON B. COHEN, CLEVELAND.—We have used some of these synthetic preparations in the nose, particularly because the supply houses have told us that they were not irritating, and we have found several patients in whom there have been very severe irritative reactions in the nose, quite like those seen from ephedrine, so we cannot believe that these symptoms "never" occur. One hundred per cent values do not exist, even with ephedrine.

DR. KERN.—In regard to the question raised by several gentlemen as to the exact nature of the particular preparation used by us: Chen and Schmidt classify the *synthetic* products in two groups: (1) *dl*-ephedrine, a substance which has the same chemical structure as natural ephedrine, but is a racemised product consisting probably of equal parts of *d* and *l* ephedrine (the natural drug is optically active and levorotatory); the substance that we used is of this type. (2) A group of ephedrine-like substances, which are similar to but not the same as ephedrine (Chen and Schmidt place in this group the product studied by Dr. Piness, nor-ephedrine).

We used the one we did simply because it appeared to be the nearest thing to the natural drug.

It has been possible to test the physiologic effect of levorotatory ephedrine and of dextrorotatory ephedrine. Theoretically the synthetic *dl*-ephedrine should be slightly less active than the natural *l*-ephedrine. This, in general, falls in with some of the effects we have noted, as for example on blood pressure.

We gave the drug in the manner that we gave it and in the dose that we used not because we were trying to find out the effect of ephedrine and its related substance on bronchial asthma—there is plenty of information on that point—but because we wanted to compare the effect of the synthetic drug with that of the natural drug by using them in exactly the same way.

I agree fully with what has been said about the effect of the drug or its lack of effect in different cases and its various indications, but that is aside from the point. We were making a comparison between two substances, not a study of a new substance. With that in mind I also want to emphasize that we have not claimed that the synthetic drug is a substitute for the natural, but an addition to our therapeutic armamentarium, in that we found that some patients can take one and some the other. I do think it is worth while bringing this to your general attention.

In regard to dermatitis, this did not occur in any of our patients so I have no experience with what Dr. Davison asked about.

In regard to the patients who were made worse by ephedrine, one had normal blood pressure and the other showed a histologic observance of 160. The outstanding thing was marked emphysema with obvious circulatory embarrassment.

So far as constipation goes, I mentioned digestive tract symptoms "nausea, vomiting and others," which included abdominal pain, and constipation in a few instances, though we did not note it with the synthetic drug, whereas we did note it in one or two cases with the natural drug.

I fully agree with Dr. Cohen that we got almost as much irritation with one as the other when used intranasally.

DR. SCHENCK.—Lack of time prevented our mentioning the local effects of the two drugs. A galvanometer, screen, potentiometer and thermocouple—of which the thermocouple was the most important item—were assembled, and the actions of 3 per cent aqueous solutions of ephedrine and of synthetic ephedrine were compared. The results were noted by the beam of light thrown on a screen by the string galvanometer. We have not made sufficient estimations to obtain conclusive results. In 15 individuals, 12 showed equal effects with the two drugs, and 3 indicated slight advantage on the part of natural ephedrine. However, 15 cases cannot be used for basing final conclusions.

The present cost of the two is the same—two dollars an ounce. The reason for the cost of the synthetic drug at present, at least in this country, is its limitation to research and small scale production. When put on a commercial basis and manufactured in large amounts, it will be comparatively cheap. No manufacturer has a monopoly on production as the drug has been synthesized by twelve or thirteen individuals. Three or four firms have produced the synthetic product; no one can corner the market and cause price inflation.

Studies in Asthma XVI. Two Hundred and Thirteen "Cured" Cases, Followed Up Again Four Years Later. F. M. RACKEMANN, BOSTON, MASS. (For abstract, see Vol. 3, page 515.)

DISCUSSION

DR. WARREN T. VAUGHAN, RICHMOND, VA.—First I want to express admiration for Dr. Rackemann's follow-up. Being able to get definite follow-up information on 88 per cent of the cases in any series is really a very remarkable achievement. He has such a well organized follow-up that I hope some time he will be interested in conducting a similar survey on the residue cases in his first column, those who had no benefit, and find out what has happened to them in the meantime.

One additional thing that occurred to me when he was talking was the surprising way in which, in his cardiac asthma groups, there was also a high percentage of allergic family history and personal history; high eosinophilia, and some rather frequent positive skin reactions.

I wonder whether Dr. Rackemann would classify those as cardiac asthma or as cases of cardiac asthma with a concomitant allergic factor, or as cardiac asthma with no allergy.

DR. GEORGE PINESS.—I hope Dr. Rackemann will bring out how many of the patients with cardiac asthmas died in the four years, which would give us some information as to the prognosis we could give these patients.

DR. RICHARD A. KERN, PHILADELPHIA.—I should like to ask the criteria for the diagnosis in cardiac asthma, and as to whether some of these patients might not have been individuals with cardiac disease who

happened to be asthmatic, a condition which in general medical practice is only too frequently overlooked.

I have seen and reported several such patients in whom the history and the whole clinical picture were that of cardiac disease but in whom in one instance the wheezing character of râles pointed to the probability of asthma, and in another, an unexplained eosinophilia led to the same conclusion. In each a greater search uncovered allergy, with resultant continued improvement in the general state when the allergic factors were attended to.

DR. MILTON B. COHEN, CLEVELAND.—It seems to me that studies of this sort illustrate very well the importance of following patients long enough really to know what happens to them. I am very much impressed with the fact that the patients who were cured of their asthma or whatever manifestation they had, later developed certain other manifestly allergic symptoms.

I think it is very important for those of us who take care of this type of patient to make arrangements with our patients so that we can see them long enough really to know what is going on, and it may well be that if this perennial treatment of hay fever does not do anything else than make possible their coming in often, it may justify its existence even though the results may not be any better than with the preseasonal type, simply because we are able to follow our patients long enough.

If a patient who is cured of one type of symptom goes along and develops another, that is part of our job. We should be following the patient so that when the new symptom comes we are ready to recognize and follow it up.

DR. GEORGE PINESS, LOS ANGELES.—I think we are wrong in using the word "cured." I think we should limit ourselves to "symptom free," because the comeback is bad. If we told patients they were "symptom free" they would not be positive they were "cured." I think if we should say "free of symptoms," we should probably use a better term.

DR. ALBERT H. W. CAULFEILD.—I am sure that Dr. Rackemann in following this up must have got a lot of information he has not given us, along many lines, and I should like to ask particularly, as he mentioned one patient had a kidney removed, and so forth, if he got any previous reports as to whether any other type of diagnosis had been made, or they were still under treatment, or if any other condition was discovered.

DR. HARRY S. BERNTON, WASHINGTON, D. C.—In connection with the use of the word "cured," I should like to remind the society of what Oliver Wendell Holmes said in his delightful volume of medical essays, "to cure a patient is to care for him."

DR. FRANCIS M. RACKEMANN.—Of course, the word "cure" ought always be in quotation marks. There is no question about that. There is exactly one patient in this series of more than a thousand cases that we are quite sure is cured in the allergic as well as in the clinical sense.

As for cardiac asthma, the diagnosis to me is always difficult. It is based on two principal points. The first is that the onset of cardiac asthma occurs after the age of fifty years and in men more often than in women. The second is that the first attack and subsequent attacks are often and usually brought on by exertion. Incidentally, patients with cardiac

asthma sleep well at night as opposed to the other patients with bronchitis and other forms of asthma, whose nights are bad.

Finally, there is a distinction between the effect of morphine, which is good in the cardiac cases and rather bad in the other straight asthma cases.

As for the late results in the chronic bronchitis and emphysema cases, I have not as much information about that as I should like. I do not know that any number of them have developed tuberculosis. The follow-up has been based chiefly on letters, and I have actually seen and examined these people only in a few instances.

An Estimate of the Ketogenic Diet in Bronchial Asthma. H. L. ALEXANDER, ST. LOUIS, MO. (For original article, see page 26.)

DISCUSSION

DR. GEORGE PINESS.—Dr. Alexander brings out very forcibly again the question of juggling our asthmatics with diets. I think this question of ketogenic diet is no different from all the other diets that have been presented to the profession at large.

In this particular case where he presents an individual who is improved by being put on an elimination diet, he also mentions the fact that this individual was sensitive to milk. If this same individual were taken off milk and given a rational diet, he probably would have gotten along just as well, and it is my opinion that all diets are of very little value, and what value there is to them is dependent entirely on two factors: first, the specific knowledge that an individual is sensitive to certain things which are eliminated from his diet; and, second, the information that you get from the patient in which he tells you that there are certain things he cannot take, and those are the things which should be eliminated from one's diet, thus making an elimination diet comparable with the patient's diet from the specificity standpoint, and also from what we have learned from patients in which they themselves know that they are sensitive to certain things, and the fact that they dislike them for that reason, or that they do produce symptoms.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—Dr. Alexander has inadvertently overlooked a paper published in 1930 by Dr. Fineman and myself on "The Rôle of Ketogenic and Low Carbohydrate Diets in the Treatment of a Selected Group of Asthmatic Children." In our series the patients selected for treatment were those in whom the asthma remained severe, persistent and of long duration in spite of treatment according to the accepted standards of modern investigation and management. These children had been under observation for over two years when treatment with the ketogenic diet was instituted. No drug, injections or other therapeutic measures were employed. The various foods known to cause symptoms of allergy in these patients were eliminated because an attack of asthma resulted in every instance when such foods were ingested, in spite of ketogenic diet.

In these children with chronic refractory asthma, the ketogenic diets alone have proved efficacious to the extent that the chronic asthmatic state in the majority of instances was controlled or entirely cleared up, at least for a sufficient period of time to permit such a child to get its bearings. In other words, the ketogenic diet affords a plan of treatment which only tem-

porarily controls a bad situation. Its action is comparable to that of the various nonspecific therapies. In children with hay fever and pollen asthma and in the asthma of adults, the ketogenic diet was found to be worthless. We also stressed the fact that these diets were not "elimination or trial" diets and should not be confused with them.

During the period when the children were free from asthma, skin tests were performed and the size of the positive reactions obtained was found to be no different from the size of those done prior to the institution of the ketogenic dietetic treatment.

Ketosis, per se, apparently does not account for the results obtained, since definite improvement or relief from asthma also occurred in some children in whom acetone in the urine could not be demonstrated.

The children were not hospitalized. They were permitted to live at home and carry on in their accustomed habits.

The ketogenic diet does not replace by one iota any form of specific desensitization therapy. As a matter of fact, we maintained that the ketogenic diet, on account of its extreme formula, is a dietary "stranger" to the allergic person and may be considered, for children, as a form of nonspecific treatment capable of inducing physiochemical change via the alimentary tract.

DR. MILTON B. COHEN.—It seems to me that Dr. Alexander's work brings out the importance of going back to more or less fundamental observations and then trying to apply them in controlled practice as nearly as one can control them.

You may do an experiment on a dog and get a certain result which points in a certain direction. Then you attempt to apply it clinically, and, if you are not careful, you are inclined to draw conclusions which would not be justifiable in this instance.

I do not want these remarks to be taken as a criticism in this instance; in fact, I intend them to be quite the contrary, that here we are dealing with the controlled thing. I am reminded of the fact that quite similar results are obtained when one tries certain other clinical applications of laboratory procedures.

We conceived the idea that because a good dose of strychnine in an animal will increase the epinephrine output, we might be able to control patients with asthma by giving strychnine enough so they can produce their quantity of epinephrine and keep it high enough to keep them well. Unfortunately, we found out we would have to give enough to kill a man in order to cure him with the epinephrine which he would put out. We cannot get enough ketosis to keep the man alive to get the same effect that we have in the dog.

DR. WARREN T. VAUGHAN.—Two years ago in Detroit we were told that allergy was due to an alkalosis, and we were told that we must give hydrochloric acid to relieve the alkalosis and thereby relieve the allergic manifestation, and we were given figures that were truly remarkable for results, just as good as any with the best methods of allergic therapy.

I think we are very fortunate today in having had a real study and presentation of the question that was raised at that time. We have been arguing back and forth, but this presentation really gets down to the bottom of the thing.

Dr. Alexander has shown us that there might be some logic to the assumption that we are dealing with an alkalosis, or at any rate that an

acidosis might relieve the condition, and has at the same time shown us that for practical purposes we cannot rely upon it.

DR. ALEXANDER.—In so far as the studies of acid-base balance go, and the determination of the P_H in the urine, we determined the P_H values in the blood, which is more significant. I think it is generally accepted that a ketogenic diet does not produce a very marked acidosis. We did attempt to estimate a ketonemia, but I am afraid that our method which we used and our inexperience make it not sufficiently reliable, but we did a critical thing. We took the P_H of the blood, and any acidosis which gets beyond the buffer substance of the blood to reduce the P_H is a real acidosis, and our P_H values did not vary a bit, nor the CO_2 combining power, which went down very little. We thought that adequate.

As far as the ketogenic diet's being an acid diet, I think that is well enough known.

I did commit an oversight and I should at the outset have stated that these were adult patients, and that is our only experience. I am well enough acquainted with the work of Dr. Peshkin, which is very encouraging, but it is so much easier to give an acidosis in children than in adults, and we are merely reciting the experience we have had in them.

Is Allergy a Factor in Angina Pectoris and Cardiac Infarct? G. WERLEY, EL PASO, TEXAS. (Abstract.)

On the theory that the vascular reactions due to allergy include spasm of the arterioles, and at times, perhaps, spasm of arteries, the author predicates the possibility of coronary constriction from the same cause. Many authors are cited who have recognized the association between indiscretions in eating and attacks of angina pectoris, which suggests that food allergy may underlie the cardiac condition.

A series of 62 cases of angina pectoris and cardiac infarction were studied in relation to food allergy. Personal histories and skin tests indicated that 96.8 per cent of the patients were allergic to one or more foods (Table I).

TABLE I

62 CASES OF ANGINA PECTORIS AND CARDIAC INFARCT

	NO. OF CASES	WITH HAY FEVER	WITH ASTHMA	WITH FOOD DISAGREEMENTS	WITH URTICARIA	WITH ANGIONEUROTIC EDEMA	WITH MIGRAINE	OTHER MANIFESTATIONS	NEGATIVE PERSONAL HISTORY	FAMILY HISTORY OF ALLERGY	GREATLY IMPROVED BY DIET	ELECTROCARDIOGRAPHIC EVIDENCE	DIED
Angina pectoris	34	6	6	22	11	6	17	7	1	11	14	6	
Cardiac infarct	28	1	5	20	9	1	17	7	1	14	13	19	11

Specific examples of the association of food allergy with coronary manifestations are stated. In one patient, sensitive to 7 common foods, dietary corrections relieved anginal symptoms. In a similar patient who gave 13 positive skin reactions to foods, anginal attacks disappeared after dietary adjustment. In one case during an attack angioneurotic edema and migraine, substernal pain occurred, and an electrocardiogram taken at the time showed definite changes in Lead I, which disappeared one week later. A similar case is cited wherein at the height of an attack of urticaria with angioneurotic edema due to strawberries, severe angina pectoris occurred which was relieved by nitroglycerin. Other cases are reported.

The association of angina pectoris and migraine (55 per cent in this series) noted by various authors is recalled.

No blood eosinophilia was found.

It is emphasized that elimination of foods to which patients were allergic has resulted in relief from angina pectoris. Return to these foods has caused a return of angina, with relief again by their elimination.

Functional Cardiac Disorders Caused by Sensitiveness to Heat or Cold.

W. W. DUKE, KANSAS CITY, MO. (For original article, see page 38.)

DISCUSSION

DR. F. W. GAARDE, ROCHESTER, MINN.—I should like to ask both Doctor Werley and Doctor Duke whether, in conjunction with the elimination of food to which the patient was sensitive, anything else was done for these patients in the general management of the cardiac condition. This question is rather important, I believe, as most angina and functional cardiac disorders can be fairly well controlled by the general management, particularly in the early case.

DR. RAY M. BALYEAT.—If I remember correctly, Dr. Werley spoke of migraine cases associated with angina. I think, though I am not sure, that we have seen no patient suffering from migraine who had angina. Is that right, Dr. Rinkel?

DR. RINKEL.—Yes, that is correct.

DR. BALYEAT.—Recently we had a woman, fifty-seven years of age, with angioneurotic edema who suffered from severe attacks of angina. At times the angioneurotic edema would be severe on the days she suffered from the anginal attacks, but she would also have severe angina attacks without evidence of angioneurotic edema.

Recently we saw a doctor suffering from gastrointestinal symptoms of an indefinite type. He reported that at times he would have many extra systoles. On one occasion three eggs were given him for breakfast, and about thirty minutes following his meal he fell on the street, semiconscious. They reported, on examining his heart, that there were many extrasystoles. On testing him he gave a marked reaction to eggs, and he reported to us, after telling him about his egg sensitivity, that as he looks back over his life, on a number of occasions he believes that egg has caused cardiac symptoms in the form of extrasystoles.

DR. ALFRED M. GOLTMAN, MEMPHIS, TENN.—I should like to ask Dr. Duke whether he thinks that giving the adrenalin was specific from

the allergic standpoint or whether giving the adrenalin and thereby increasing the heart rate, were not the reasons that the extrasystoles stopped. It is a fact that increasing the rate of the heart causes the extrasystoles to disappear.

Many extrasystoles, especially before middle life, in the absence of focal infections are often neurogenic in origin, and we have worked out a plan whereby by application of heat and cold alternating over the precordium and absolute rest, the extrasystoles disappear. Whether or not you can prove that these extrasystoles referred to by Dr. Duke are due to a specific sensitivity to heat and cold or are on another basis seems to me a rather hard thing to do.

DR. RICHARD A. KERN.—I should like to urge an extreme reticence on our part in assigning allergy as an etiologic factor in cardiac disorders. That allergic manifestations may be precipitating factors in bringing about or bringing to the surface an existing subsurface cardiac lesion is obvious, but to insist on a strict etiologic relationship I would say is totally unjustified. The very fact that such cardiac disorders, angina notably, tend to appear in an increasing incidence at a time of life when allergic manifestations, notably food allergies, are decidedly on the decline, must be given some weight.

Furthermore, I urge extreme caution in such cases of angina in which you suspect that an allergic factor may be a precipitating one in an angina: do not use adrenalin. Adrenalin is absolutely contraindicated in angina. I have seen more than one fatal coronary thrombosis precipitated by the giving of adrenalin in what was supposed to be a case of cardiac "asthma," but which was simply a case of cardiac failure.

That allergy may in some of the functional disorders play a rôle, I believe is possible. I should like to cite one case which fits that picture as well as any of which I have knowledge in the literature.

A woman now forty years of age has had paroxysmal attacks of tachycardia since the age of five years. After thirty-five years of paroxysmal tachycardia, she has an electrocardiogram which is as normal as I hope mine will continue to be. Every cardiac functional test has been applied in her case, and with normal findings, yet she can precipitate an attack by eating certain foods to which I have tested her, and to only one or two of which I got slight reactions; the rest were all negative, done by both cutaneous and intradermal testing.

One amusing thing in the case is that she has always been able to stop her attacks herself by a certain maneuver. She never bothered about going to a doctor, until on one occasion not so long ago she was in a position where she could not indulge in this maneuver without some embarrassment to herself and so the attack was allowed to go on and continued for over twenty-four hours and was finally stopped by the administration of quinidine. The maneuver was that she had to stand in this position (bending forward at the waist with arms hanging straight down and head almost touching the floor) for four or five minutes. She was at a dinner dance when this attack came on and she was ashamed to try her stunt. Since avoiding the particular foods, she has gone for a number of months without an attack. Yet even in this case I hesitate to say that allergy is the underlying cause of the paroxysmal tachycardia. It may in all likelihood be simply the spark that sets off the powder.

DR. MILTON B. COHEN.—It seems to me that we now have some fairly definite histologic ideas of what comprises allergy and that before we al-

low our wish fulfillments to make us overenthusiastic about finding new conditions that we say are allergic, beyond merely suggesting that they may possibly be, it would be well for us not only to run controlled experiments on one, or two, or three cases, but on a sufficiently large series to compare them with the ordinary incidence of changes in that particular disease, and also to make some very definite histologic studies of the materials available when we get autopsies on these patients.

Dr. Werley talks about changes in the gastrointestinal mucosa, but he does not tell us whether these changes show any of the allergic inflammatory changes. Certainly what little I have seen and heard and read of the changes in hearts in individuals who have had angina and died of other things, or individuals dying following coronary thrombosis does not seem at all like the changes seen in allergy.

I agree with the President most emphatically that this society, representing as it does, men limiting themselves more or less to allergy, should, rather than add new conceptions, attempt and insist that these conceptions are true. I think it is a function of this society rather to debunk a great many of the things which are suggested here, there and yonder. This should be a clearing house for controlled information so that ultimately other societies and organizations and individuals may get definitely controlled facts on which to base their further studies.

DR. G. WERLEY, EL PASO, TEXAS.—As to whether we did anything else besides eliminating foods, of course we *did;* but my impression is that when we eliminated all foods to which the patients were allergic we saw improvement that we had not seen before.

I welcome Dr. Kern's criticisms. One will not find what I found in my cases unless he searches with allergy in mind. So good an observer as Sir James Mackenzie missed it because he failed to look for it. I believe that my critics will change their minds as they study angina more carefully and test for allergy in their cases. I stated carefully, I thought, that allergy was only a factor. Dr. Kern admits that much when he says that it could be a precipitating factor. He has aptly remarked that it is the spark that sets it off.

Dr. Hoffman's experience with adrenalin and angina is very interesting. The explanation of conflicting results may be in the dose, small doses giving relief and large doses even precipitating the attacks.

It is true that angina does not depend entirely upon age, but in our cases we found food allergy in practically every case, and in the 18 cases that were skin tested every single one reacted, so that in angina at least, allergy seems to increase with age.

I have had cardiac infarct myself, and since then a violent attack of urticaria and a seizure of angina at the same time. Angina pectoris and cardiac infarct are distinctly different clinically, but I do not think the etiology is different fundamentally. Infarct is only a late happening in the course of the same thing that is producing angina pectoris, viz., coronary sclerosis, with the acute attacks precipitated by allergy, the emotions, etc.

Dr. Cohen is right that the postmortem material should have been studied more carefully. The bodies were embalmed and that seems to interfere with staining for eosinophiles. One finds very little tissue work on allergy in the literature.

I am well aware that this subject needs more study. I know that the road of medical progress is strewn with the wrecks of theories.

DR. W. W. DUKE.—In closing I wish to compliment Dr. Werley in his work and say that I hope we hear more from him along this line.

I should like to ask Dr. Cohen why he assumes that the heart muscle is immune to hive reactions or why it is immune to the effect of vagotonic reactions characteristic of generalized allergy. Is the heart different in this respect from other tissues? I personally do not see why any active living tissue should be immune to the effect of allergy.

DR. MILTON B. COHEN.—I do not say you cannot, but I want evidence that you can.

DR. DUKE.—The allergy lesion consists of a local lesion, the hive, and in addition, to a more or less general vagotonic condition which can effect organs as influenced by overactivity of the vagus nerve. We know the latter can precipitate irregularities in the heart. We know further that you can precipitate irregularities in the heart with adrenalin. I have frequently noticed cardiac arrythmia, tachycardia, and anginal pain in allergy patients coincident with other allergic reactions. In this paper I have described irregularities which can be precipitated by heat and effort on one hand or cold on the other and relieved by the reverse condition.

The treatment of cases of this sort has been very successful in my hands and, like treatment with pollen, consists in the beginning in avoidance of overexposure to the agent which makes the patient sick and, finally, getting them tolerant of the agent which makes them sick. The result, especially in cold sensitive cases, compares very favorably with successfully treated pollen cases.

Dr. Kern has warned us against the use of adrenalin in angina pectoris. I have been careful with the use of adrenalin because of fear of the effect of adrenalin on anginal cases. However, I have used it in anginal attacks and in cases of extrasystoles in allergy patients with complete relief. The effect of adrenalin can be so controlled with the use of a tourniquet that I do not have the fear of it which I had formerly. The tourniquet will reduce a marked adrenalin effect in about thirty seconds. Whether or not the extrasystoles could have been due to a change in the heart rate was taken into consideration at the time we were making examinations. If there was any change in the rate, it would not amount to more than three beats per minute. I should like to ask Dr. Kern if he tested his patient who had tachycardia since childhood for sensitiveness to heat or cold.

DR. KERN.—No, Doctor.

DR. BERNARD KAUFMAN, San Francisco.—I appreciate the courtesy of being allowed to discuss this subject, and I should like to say a few things in regard to Dr. Duke's paper.

Having an interest in cardiology and being a little unorthodox, the same as Dr. Duke is, I was anxious to hear Dr. Duke's statement as to the etiology of what I am inclined to call precordial pain rather than angina pectoris. Personally I think Dr. Duke has contributed something in his experimentation which will have a vast influence on medical thought.

I think perhaps he does not realize that the conception of angina pectoris and that of coronary occlusion are being sharply differentiated from one another. There are at least fourteen different diagnostic points between the two of them, and the tendency is now, I believe, to bring the two things separately and to dissociate angina pectoris or precordial pain from organic heart disease itself.

There was a paper given recently in which McCrea, of Philadelphia, stated that the only theory not advanced for the origin of angina pectoris was that of the nerve theory. That seems to have been advanced by others.

The question of angina pectoris in respect to age bears no part. Age does not enter into it at all. It was originally described by Heberden as occurring a child twelve years of age, and cases under the age of twenty-five years are not rarities; there is thus no doubt that the age is not a factor at all.

The question of allergy entering into it I am unable to discuss adequately because of the fact that my practice has not brought me sufficiently in touch with that phase of it, although Dr. Matzger, in my city, has made me interested in the subject. However, if I might take issue with the President in respect to the dangers of adrenalin, I would say it is true that Dr. Levine, of Boston, has reported a death in Boston in using adrenalin to differentiate between angina pectoris and coronary occlusion, but adrenalin dilates the coronary arteries and is not a dangerous drug in the use for which it is indicated. It is definitely indicated in the treatment of coronary occlusion, where one can dilate the remaining coronary vessels which are not occluded and give a more adequate blood supply to the rest of the heart muscle.

So, the statement of the President, while in certain cases is true, yet in general is not to be taken too generally, I think, whereas Dr. Duke's statement about heat and cold is not a new statement, that is to say, it has been described by Nothnagle about the year 1880. He did not do the experiment in the way Dr. Duke has produced the pain, but he had never carried the experiment further and produced relief toward heat and pain, and from that point of view I think Dr. Duke's statement today will go into medical history as representing a new phase in our conception of angina pectoris.

Urticaria—Etiology and Treatment, With Special Reference to Autohemotherapy. R. M. Balyeat and E. M. Rusten, Oklahoma City. (Abstract.)

Urticaria is defined and classified both morphologically and etiologically. Only 60 per cent of cases of urticaria are due to allergy. The cause of the remaining 40 per cent is varied and often difficult to find. Frequently the skin manifestation represents an internal lesion, and consequently all cases merit a thorough medical examination. A case in point is cited, wherein urticaria was apparently due to Hodgkin's disease. The wheals disappeared under x-ray therapy to the glands and reappeared with exacerbation of the disease. In another patient allergic to foods, urticaria seemed to be immediately associated with hyperthyroidism in that it disappeared as the metabolic rate approached normal. The foods giving skin reaction could then be taken in moderation without urticaria. It is believed this type of patient who can tolerate moderate quantities of food to which he is sensitive unless he encounters some secondary factor, is not uncommon.

Prodromata were present in 51 per cent of a series of 125 cases studied by the authors. They include the following: headaches, upper abdominal pain, frequency and urgency of micturition, diarrhea and constipation.

Cases of urticaria due to contact with feathers are described; likewise from contact with novocaine; and one due to epinephrine taken hypodermically. The latter patient likewise developed urticaria after taking aspirin and ephedrine by mouth. This manifestation did not occur when foods to which the patient was sensitive were eliminated from the diet.

In determining the cause of urticaria, scratch and patch and clinical methods of testing should be used. In the majority of patients suffering from urticaria due to specific sensitization to food, one can demonstrate by either the scratch or the intradermal method of testing, a positive reaction. Occasionally no skin reaction will appear in such cases.

Successful treatment depends upon the proper evaluation of the history and physical examination. The acute cases are for the most part self-limited. In cases of allergic origin one must take into account both the primary and the secondary factors.

Autohemotherapy has been used by the authors in 27 cases of chronic and acute urticaria. Ten cubic centimeters of the patient's whole blood were injected intramuscularly every two to four days. In 24 cases symptoms were relieved in from thirty minutes to two hours for a period of two to four days. Some patients after three to four doses remained free for two to four weeks. The mechanism involved is not known.

DISCUSSION

DR. LEON UNGER, CHICAGO.—This subject of autohemotherapy has interested me a little, especially because of Pasteur Vallery-Radot's book on urticaria. He puts autohemotherapy down toward the bottom of his treatment. He puts peptone way up to the top, and all of us have tried peptone with varying success.

I have tried autohemotherapy on two patients within the last month, with no improvement at all in the first case, and the second case became distinctly worse after injection.

There is another point in Dr. Balyeat's paper that I wish to mention and that is the use of the words "hay fever." Dr. Balyeat uses that term "hay fever" when he speaks of egg, that the patient gets "hay fever." I think we should restrict that word to pollinosis and use the words "symptoms of rhinitis, vasomotor rhinitis," rather than the term "hay fever," simply restricting that to the pollen cases.

DR. M. MURRAY PESHKIN.—Urticaria has been an interesting and confusing subject to me. The symptoms are unquestionably allergic in origin. We know urticaria may be caused by either contact with or ingestion of the offending substance. The offending substances are regarded as the primary exciting factors. Patients with urticaria, like those with asthma, may also suffer attacks resulting from various nonspecific (contributary) causes such as overexertion, insufficient rest and sleep, worry, stress and strain of life.

All the papers on urticaria that have come to my attention treat this subject without reference to its relationship to other allergies. The impression is gained that the patients reported suffered only with urticaria. The incidence of positive protein skin reactions reported may be high or

very low, while some authors report no cases with positive reactions, and believe that urticaria behaves like a nonallergic condition.

My understanding and management of urticaria have been made easier since I classified urticaria into primary and secondary groups. Primary urticaria occurs in an individual who has no previous existing allergic syndrome. Secondary urticaria occurs in a patient with a history of preexisting hay fever or other allergic condition. The protein skin reactions in patients with primary urticaria are invariably negative. The bulk of the positive skin reactions obtained in urticaria are in those patients suffering with the secondary type. This type of urticaria, from a clinical standpoint, behaves and appears to be different from the primary type.

It is possible that the mechanism behind primary urticaria with its refractory skin reactions, is not identical with that operating in the secondary type. This is merely a speculative thought which may engage your attention.

Urbach recently advocated the use of propeptones in various dermatologic conditions. It seems that he is now coming to the conclusion that the only real use for propeptones is in cases of lichen urticatus—a form of urticaria always demonstrating negative protein skin tests and extremely resistant to dietetic treatment.

When some form of nonspecific treatment is employed to the exclusion of dietetic and other measures in a patient with an allergic ailment, it is tantamount to a confession of our inability to cope with the situation. Experience has taught that nonspecific therapy at its best is merely palliative and the temporary relief from symptoms occurs for short periods of time. For primary and secondary urticaria, the best results I have thus far obtained involved a treatment in which a diet best suited for the patient, and, whenever possible, restriction of the known contributory factors.

DR. GEORGE PINESS.—First I want to ask Dr. Balyeat what his percentage of food reactions were, obtained in urticarias, what percentages he got—nothing but foods. Second, I want to try to clarify this business of angioneurotic edema and urticaria. I think they are two separate and distinct entities, that the angioneurotic edema is not allergic. The true edema is not allergic edema, and in some of the angioneurotic edema so diagnosed in some of the cases seen by Dr. Balyeat and perhaps myself, they were nothing but giant urticarias and they have no relation to the subject discussed.

As to the cases of aspirin, I think the most severe cases I ever saw were due to aspirin. Why, I do not know. Again, another interesting thing, and again, why, I have no knowledge, is the number of cases (since Prohibition) that have been due to gin. I do not know how many have noted that peculiarly interesting story of having a urticaria following the ingestion of gin. Why, I do not know. I wish I did.

Using adrenalin as a palliative measure is like throwing water into the sink because the relief is so temporary, the time of relief is so limited, and the persistency of the symptoms so prolonged that you get very little out of the use of adrenalin. I find that most patients get nothing but a pallor and a temporary relief lasting from a few minutes to perhaps an hour.

Autohemotherapy is not new and in all the reports that I have been able to get from men who have tried it—not who have published it—the results

have been flat failures and that is true in my own experience, in those cases in which we tried it, not because we believed in it but because it was forced upon us—somebody had it and thought thus and so—these all resulted in failures also.

The natural answer to it is this: Anything that you use sometimes gives results, and there is no specific therapy in giving autohemotherapy.

DR. C. ULYSSES MOORE, PORTLAND, OREGON.—I wish to thank Dr. Balyeat for the many suggestions he made and to say that if his suggestions prove true, he has made wrecks of a lot more of our present theories.

I wish to ask him about a certain procedure that is being used by a very able and reputable man in our town who claims he can cure all cases of urticaria by making a vaccine from the patient's stool and giving him this vaccine treatment. How do you explain the fact that he is getting results?

Doctor Balyeat brought out the idea of congenital pyloric stenosis being associated with allergy. I should like to ask if he has produced it experimentally? In our research work at the University of Oregon Medical School, we have produced pyloric obstruction in young rats born of mothers fed on insufficient amounts of vitamin B. By applying this treatment to human mothers we seem to be reducing the amount of pyloric obstruction among the babies.

It raises the question: Is there a possibility of a relationship between vitamins and allergy?

DR. HARRY S. BERNTON, WASHINGTON, D. C.—If I interpret correctly the feelings of the authors, there seems to be a very frank expression of helplessness in the treatment of urticaria. Under the conditions, it may not be amiss for this society to appoint a committee to investigate the subject.

I have had the opportunity to study a patient who was subject to giant hives of a most aggravated type. I tested this patient intracutaneously with her whole blood and with her blood serum—both of which were collected at the height of an eruption. I also performed a skin test with extracts of her stools and of urine, with the hope of reproducing wheals, but with negative results. I have, also, been able to secure in pure form all food proteins which have thus far been isolated. I have used them in the testing of patients with urticaria.

All of our observations have been essentially negative. I have been very much interested in learning something about the treatment of hives.

It is in virtue of my disappointment, Mr. President, that I again urge you, with your usual wisdom, to appoint a committee.

DR. HAL M. DAVISON, ATLANTA, GA.—It is requested that Dr. Balyeat give us his experience with the contact test in urticaria.

DR. I. S. KAHN, SAN ANTONIO, TEXAS.—Speaking from personal experience with an attack of severe food urticaria which necessitated a three-day hospital residence, I can confirm Dr. Piness' statement that adrenalin relief is of only very brief duration. I found also that scratching one part of the body, increasing at once the general eruption, was the most deleterious of the physical agents experimented with, and in spite of catharsis and omission of all foods. No relief was secured until this had been eliminated by the use of codeine.

DR. RAY M. BALYEAT.—In regard to Dr. Unger's question about the value of autohemotherapy, we had never used such therapy until recently.

Dr. Rusten, who is with us, had used it a great deal in skin conditions and insisted on our using it. We had on hand so many patients with hives; some of them were doing fairly well and some of them were having difficulty. He insisted on using the therapy in hives, and certainly in some cases it is treatment well worth using. In some cases no results were obtained but in others it has been very gratifying. Relief in some cases lasted only a few days, but in others has lasted many days. The great advantage in the procedure lies in its simplicity and its safety. No untoward reactions have been noted. We reported two cases in which no results were obtained. Dr. Unger is not justified in condemning its use because he did not obtain relief in two cases, as the third and the fourth might have been cases on which good results would have been obtained.

In the treatment of urticaria, adrenalin, as in the treatment of asthma, is only palliative, but it is well worth using. For example, in a patient who suffers severely at night adrenalin will give him relief from his asthma, sometimes lasting one hour, but sometimes five hours, and sometimes carrying him through the night. The same is true of urticaria.

In regard to Dr. Peshkin's remarks relative to secondary factors. In hives we consider the sensitivity is the underlying or primary factor; and the stress and strain of life, anger, excitement, etc., as the secondary factor. We all have seen asthmatics who are sensitive to pollen, who have no asthmatic symptoms until the cold air strikes them. The cold air acts as a secondary factor. I have a patient in mind who is sensitive to a food and can eat that food without difficulty as long as she does not get excited or become angry. Anger will change the system in some way, probably changing the metabolism of the body so that the food will precipitate hives.

In testing patients with hives we find some of them give good reactions by the scratch method; others require the intradermal method to find the positive food factors.

Dr. Moore brings up the question of vaccine. There are certainly some patients suffering from hives, nonallergic in type, that is, at least no positive food factor can be determined, who will do fairly well on vaccine obtained from stool cultures.

As to pyloric stenosis due to allergy. In our own city there is a little boy whose case I want to mention. A diagnosis of hypertrophic pyloric stenosis was made by an excellent pediatrician and a very conservative surgeon. The boy was operated at three weeks of age, but continued to have his symptoms. Four years later he was operated again, thinking they had overlooked his stenosis. Nothing was found. The pediatrician brought him for testing because he had evidence of egg sensitivity. We found that his mother had eczema—had been a patient of ours several years before—his aunt has asthma and his grandmother has migraine. He was found definitely sensitive to egg and egg was removed entirely from his diet, with complete relief from symptoms, and he has remained free for a number of weeks.

A Case of Urticaria Due to Insulin Sensitization. MARION T. DAVIDSON, M.D., BIRMINGHAM, ALA. (Abstract.)

R. A. W., white, aged sixty-five years, was seen May 2, 1932, in the Birmingham Baptist Hospital suffering with severe urticaria, of five days' duration. She had been in the hospital for three weeks under treatment

for diabetes. Insulin and diet had been started on the first or second day of her stay, and she had taken ten, then twelve, and then fifteen units three times daily for about two weeks before the eruption developed.

Four years before when the diabetes first was diagnosed she had been given six doses of insulin, but had had no further insulin treatment from that time until the present. She had also followed the diet prescribed at that time only spasmodically, since. She had no urticaria then or at any other time in her life until the present attack. There is no allergic history either personal or family.

The skin tests to foods were all completely negative especially egg, wheat and milk, beef, pork and lamb, which tests were made intradermally.

Iletin, Lilly, U. 40, insulin, Squibb, U. 40 and iletin, Lilly, U. 20, all gave very marked intradermal reactions. The Lilly Laboratories were wired concerning this case, and a special preparation of iletin was sent by air mail. This was said to be made from pig glands instead of the beef glands of the usual product. This special preparation, though only U. 20, gave just as marked reactions as the others. A 1:100 dilution of the special preparation diluted with normal salt solution gave a moderate plus reaction intradermally. Several different batches of Lilly's iletin were tested and all reacted equally. Insulin Mulford U. 20 gave a marked reaction.

The iletin was discontinued and since the patient has remained sugar free for several days, it is hoped that its use will not be found necessary. The urticaria subsided within twenty-four hours after the discontinuance of the insulin. Desensitization treatment is under consideration, and the decision as to its use will depend upon the course of the case in the near future.

Several tentative conclusions seem permissible from this case. First, insulin or iletin is an antigenic substance, that is, it is protein in nature. Second, it is capable of sensitizing patients just as any serum or other protein solution. Third, all patients should be tested intradermally with insulin or iletin before treatment is begun; especially is this true where interruptions occur in the series of treatments.

DISCUSSION

DR. F. W. GAARDE.—We had a very interesting case of insulin sensitiveness at the clinic. We had been able to control the patient's diabetes fairly well without the use of insulin, but acute cholecystitis with jaundice developed and, conservative treatment being of no avail, surgery became necessary and urgent. We felt that, without the use of insulin, she would not be a safe surgical risk. Skin tests were done with the meat extract of various animals from which insulin is obtained, with no definite results. Dr. F. N. Allen obtained some pure insulin in crystalline form, but she was sensitive to it also, and, by this time, her condition was becoming critical because of the gall bladder infection. Dr. Allan then began with an

extremely small dose of insulin, gradually increasing it so that within forty-eight hours a tolerance had been developed sufficient for the patient to be given insulin to control the diabetes, and the operation was carried out successfully, which probably would not have been the case without the advantage of insulin.

DR. ROBERT W. LAMSON, Los Angeles.—There have been a number of such cases reported in the past few years, the most recent was but a few weeks ago. Tuft refers to some of the earlier case reports and adds another to the list.

Dr. Grishaw, who is associated with Drs. Smith and West in Los Angeles, has reported a case in which not one brand of insulin but two gave an allergic skin response. One brand was found which did not give any reaction. The patient failed to react to beef, pork or veal protein. A purified beef insulin failed to produce urticaria but the stock beef insulin sold by the same company gave positive reactions.

It was demonstrated that the active substance, probably protein in nature, could be removed from the solution by precipitation with acetone. Coincident with its removal all of the insulin effect in animals was shown to be absent.

I think this case is undoubtedly of interest. Just how significant it may be in the large mass of people using insulin, it is hard to say.

DR. DAVIDSON.—I noticed the report to which you referred, Doctor, and I think the conclusion drawn in it was that the reaction was due to some extraneous protein in the solution and not to the insulin itself. My idea in reporting this case was that we had positive tests to several different specimens of insulin. The products of all the manufacturers of insulin that we could get hold of gave the same reaction. While I am sure that it is quite possible that all those preparations may have been made in the same way, it does not seem probable that the manufacturers of several different specimens would all have the same extraneous protein in them. This patient also was tested to beef, pork, and lamb proteins, separately, and gave absolutely no reactions to those proteins, and it looked to me as though it were more evidence that reaction was due to the insulin rather than to any other substance contained in the solution.

Unusual Cases of Migraine With Special Reference to Treatment. A. M. Goltman, Memphis, Tenn. (For original article, see page 51.)

DISCUSSION

DR. NARCISSE THIBERGE, New Orleans.—I want to confirm what Dr. Goltman says in his recommendation to use vaccine in small doses. We have been using very small doses of vaccine in the Allergy Clinic of the Charity Hospital. We do not use the intradermal test with vaccine because there is a constant reaction to vaccine, but we do use the vaccine over a very prolonged period in very small doses. It is very seldom we exceed the dose of a thirtieth of a cubic centimeter.

DR. HERBERT J. RINKEL.—I agree with Dr. Goltman's definition of migraine that were relieved by the avoidance of specific foods. That the way the term should be used. In his paper he mentioned allergic migraine. We no longer use that term, our objection to its use being that there are no clinical features of a migraine that identify its being due to allergy.

I think if migraine is due to allergy it should be stated as such, and if you are considering headaches due to allergy they should be so designated and classified according to their particular symptoms.

If one reports the relief of migraine due to allergy, the presenting symptoms should be specified because there is considerable difference in the various types of headaches. The patients who have prodromata, hemicrania, motor, sensory and vasomotor symptoms, in our experience at least, have obtained better results than those whose attacks are always without cortical features.

Relative to nasal pathology producing "typical" migraine. I have never seen a case relieved by treating the nasal symptoms. I have seen unilateral headaches alleviated by treating the nasal obstruction, but this is a different thing from a migrainous headache.

There is a distinct difference between the various headaches due to allergy, and this should be borne in mind at all times.

As to results, if you test these patients thoroughly and eliminate the offending foods, about 25 to 30 per cent of these patients never experience headache again. If you treat the same number of cases of atopic eczema by food elimination, you will not have such good results. This suggests that while food may be responsible for the headaches or eczema, the mode of reaction is different in the two cases.

I agree with Dr. Goltman that unless one can reproduce the headache by contact or ingestion of substances to which the patient is supposedly sensitive, one is not dealing with headache due to allergy.

DR. I. S. KAHN.—I might mention two differential diagnostic points in connection with these cases of headache accompanying allergic rhinitis: first, the finding of eosinophiles in the nasal discharge, and second, the relief of the pain by the oral administration of ephedrine.

DR. HARRY L. HUBER.—The statement was made that a hundredth of a cubic centimeter of vaccine was used. This has no meaning unless we know how many bacteria are in each cubic centimeter.

DR. WARREN T. VAUGHAN.—Some years ago I reported some cases of migraine. I note that he defined it as do the neurologists, and that it was a series of cases in which nothing else was done in the way of therapy. In that paper I emphasized that in the majority of cases one had to pay attention to other factors, but I am sure that if Dr. Goltman continues with his treatment of migraine, he will find cases in which specific food avoidance alone will give satisfactory relief, and I am sure others have found the same thing.

It does seem to me that the cases treated with inhalant allergens were probably not true migraine but cases of sinus blockage and I am sure we all see many of them; I do not mean all of them, but certainly it seems that some may have been.

I would recommend just a little care in drawing conclusions that are not entirely justified by the paper, and that is the conclusion that 100 per cent of allergic migraines are probably hereditary. I should like to ask Dr. Goltman whether that is an assumption or whether he feels that the paper brings out that point.

DR. ALFRED M. GOLTMAN.—I think that Dr. Rinkel's discussion shows that he has rather misunderstood the paper. I really feel as though I am capable of making a diagnosis of migraine. The definition of migraine which I gave is not a neurologic definition from my point of view,

but it is my own definition made up from cases which I have observed. If Dr. Rinkel wishes to call it a neurologic definition, it is certainly his privilege to do so. I have tried to define what has been given to us as medical men as migraine, and I have tried to study it not only from an allergic standpoint but from the standpoint of general medicine as well. I have classified migraine as I have seen it, and I believe that some cases are allergic, but I believe also that there are other factors besides allergy in a great many cases which tend to aggravate the symptoms of an allergic migraine or produce the symptoms themselves. Taking this point of view I honestly believe that relief can be given to a larger percentage of those suffering with this affliction. In answering Dr. Rinkel's query I wish to say that the term headache used by me, as I progressed in the reading of my paper, was used for brevity and in place of my definition of migraine. These were not allergic headaches but were cases of migraine due to rapid absorption of inhalants from the upper respiratory tract and causing typical migraine. There is no reason why an allergen to which a person is specifically sensitive cannot produce atypical symptoms for that allergen. By this I mean that a person susceptible to feathers may have migraine as a result of his or her hypersusceptibility to this allergen. I trust I have made myself clear.

Dr. Vaughan asked me whether or not I thought that migraine was 100 per cent hereditary. In answer to this I can only say that it is an assumption on my part and that in my series of cases a large percentage gave positive family histories of the various allergic diseases. In the other cases the family histories I obtained were negative. This may have been due to ignorance on the patient's part of the diseases in his or her family or to other causes which I have already stated in my paper. I cannot prove that migraine is 100 per cent hereditary, but I can at least conscientiously believe it. Dr. Vaughan also mentioned the fact that elimination of certain specific foods gave relief in a good many cases. I heartily agree with him and stated so specifically, but at the same time I also stated that there were certain unusual cases in which elimination of specific foods gave no relief and that in these cases treatment with specific extracts of inhalants of various types gave relief and also that combined therapy with glandular extracts in certain other cases gave more relief.

Department of Reviews and Abstracts

Selected Abstracts

Allergic Arthropathies. Pavist, J.: Gaz. d. hôp. **105**: 299, 1932.

The arthropathies of an allergic origin present clinically a great variety of aspects. The author considers the arthropathies under two general categories: (1) those of a serum origin, and (2) those of a nonserum origin.

(1) The articular disorders following serum injection usually are of short duration, consisting of pain (the predominating symptom), occasionally periarticular edema and a certain amount of hydrarthrosis and local inflammation. The symptoms soon disappear and leave no trace. However, in some cases the symptoms are much more severe, attacking the vertebral articulations, and continuing over a considerable period of time. In the opinion of several workers in this field, these serum arthropathies have a predilection for tubercular and asthmatic individuals and in general for those patients in whom the humoral equilibrium is fragile. The individual terrain is an important factor in the disease.

(2) Among the allergic arthropathies not of a serum origin, division is made into the following classes:

(a) Acute forms simulating acute articular rheumatism.

Several case reports are given wherein the patients suffered apparently from acute rheumatism. Therapy of various sorts was employed with no success. Relief from symptoms was obtained by restriction in diet of offending proteins and the ingestion of peptone before meals. Note is also made of cases in which the symptoms were elicted by the resorption of hemotomes in the blood.

(b) Allergic hydrarthrosis: (1) intermittent, (2) chronic.

The author states that he himself has never observed a case of intermittent hydrarthrosis. He reviews the literature briefly. It is a disease of middle age and attacks women more frequently than men. The knee is the focus of election; sometimes, though rarely, both knees. The attacks are severe and of a distinct periodicity, uninfluenced by rest or fatigue. The condition between attacks is normal. There are phases of remission, particularly during pregnancy. It is generally considered a vasomotor disturbance. The patients are frequently subject also to migraine, urticaria, eczema, etc. It is suggested that the evidence is strongly in favor of desensitization therapy in such cases.

A report is given in great detail of a case of chronic hydrarthrosis, ob-

served by the author. The patient became gradually so disabled that he was unable to walk. Therapy of many sorts was tried with no success; surgery was resorted to, likewise with no success. It had been observed that the patient, who was a strict vegetarian, maintained a diet high in milk and eggs. These were eliminated from his diet, and calcium and peptone were administered. Within the year, the patient was able to walk normally and to pursue his activities.

(c) Chronic rheumatism of an allergic origin.

Case reports are given in which relief was obtained by the elimination of certain proteins from the diet. It is suggested that the question of chronic rheumatism of allergic origin needs further study. The literature, to date, presents few precise accounts.

In conclusion it is stated that in spite of the diversity of the determined causes, the treatment of arthropathies should generally lie along the same lines. The pathologic terrain should first be modified as far as possible; hepatic insufficiency, obesity, dental lesions, etc., should be treated. In the absence of any definite determining cause, the diet of the patients should be examined to see that they are not surcharged with certain proteins, especially milk and eggs. Treatment should also be instituted with calcium and peptone. All therapy, however, should be carefully adjusted to the individual.

Infrequent, Previously Unreported Nutritive Allergy. Urbach, E., and Willheim, R.: Klin. Wchnschr. **11**: 1012, 1932.

Salt, sugar and organic acids, hitherto seldom considered as causes of hypersensitiveness, are shown to be offending agents. A case report is given at length of a patient who had suffered from a skin eruption following the ingestion of eggs, ham or carrots. By the aid of peptone, the idiosyncrasy against these foods was overcome, at first temporarily and later more lastingly. Further difficulties, however, arose, and these were traced to the use of salt in food. Experiments undertaken to discover whether the anion chloride or the kation sodium was the offending agent, led to the conclusion that it was anion chloride.

A case report is given illustrating a similar idiosyncrasy to sugar.

Uterine Allergy. Rowe, A. H.: Am. J. Obst. & Gynec. **24**: 333, 1932.

Attention is called to the fact that the large amount of smooth muscle and mucous membrane in the tubes, uterus and vagina suggests the probability of allergic reactions in this tract. Five case reports are given in some detail, illustrating food allergy as a cause of menstrual irregularities. In each instance, definite and lasting relief was obtained by the use of elimination diets.

It is suggested that in cases of menstrual disturbance, where gynecologic lesions of all types have been carefully ruled out, skin tests with all foods and preferably with other types of allergens should be carried out.

Therapy of Bronchial Asthma With Adrenalin and the Adrenalin Derivatives Ephedrine and Sympatol. Tiefensee, K.: München. med. Wchnschr. **2**: 1824, 1932.

Adrenalin and the adrenalin derivatives ephedrine and sympatol are next to atropine, the most potent means of therapy in bronchial asthma. The advantages of ephedrine and sympatol over adrenalin lie in the long continuing efficiency when taken by mouth, and in the low toxicity.

After ephedrine and ephetonin there are after effects which lessen the usefulness in cardiac cases. After sympatol, no ill effects have yet been observed. The administration by mouth of sympatol stands in efficiency superior to ephedrine and ephetonin if it is given at the beginning of the asthmatic attack. Given parenterally, sympatol has an effect similar to ephedrine; given intravenously, it is similar to adrenalin.

On Splenic Treatment in Allergic Conditions of the Upper Respiratory Tract. Hutter, F.: Monatschr. f. Ohrenh. **66**: 86, 1932.

The question is raised of the rôle of the inner secretions of the body in allergic conditions. Spiess is cited as having for sometime considered a disturbance of the balance of the inner glandular secretions to be a basic factor in the problem of hypersensitiveness. In this connection the action of the spleen is considered. Attention is called to the experimental work of Mayr and Moncorps on the relationship between the spleen and eosinophilia. An increased eosinophile count has long been recognized as an accompaniment of allergic conditions. Mayr and Moncorps found that an absence or decrease in splenic function was accompanied by a hypereosinophilia, and that an increased splenic activity was accompanied by a diminution of eosinophiles. Parenteral injection of protein-free spleen extract brought about a decrease in eosinophiles and in cases of dermatoses of an allergic origin, a decrease in itching and gradual cessation of symptoms without other treatment. Mayr and Moncorps concluded that there was a definite relationship between the functional condition of the spleen and allergic diatheses.

The author, in the light of these findings, considered the possible rôle which the spleen might play in allergic disturbances in the respiratory tract.

An extract (Reticulon) was made from the cells of the reticuloendothelial system. The fluid, protein-free preparation was sealed in sterile 2 cm. ampules. For injection, usually only one ampule was used; for severe cases, occasionally, two ampules. Injections were made intramuscularly in the deltoid muscle or in the gluteus muscles. In most cases one or two injections were sufficient to secure results of long duration.

Of 16 cases of allergic rhinitis, clear-cut and favorable results were obtained in 13 cases. Results among hay fever patients were more difficult to ascertain as outside factors were more complicated. However, of 11 patients, relief was obtained in 6 cases. Protocols are given.

The author considers spleen therapy to be of distinct value.

Schwartzman Phenomenon in the Rabbit Stomach. Karsner, H. T., Ecker, E. E., and Jackson, E. L.: Proc. Soc. Exper. Biol. & Med. **29**: 319, 1932.

The Schwartzman phenomenon is produced by injecting a potent bacterial filtrate into the skin, and about twenty-four hours later the same filtrate is given intravenously. A few hours later a hemorrhagic necrosis occurs at the site of the skin injection. Very little data is available concerning the reaction in internal organs.

The stomach of rabbits was exposed by operation and an injection of a concentrated toxic filtrate of *B. coli* was made into the submucosa in a series of animals. A skin injection was made at the same time. Twenty-four hours later the filtrate was injected intravenously. The animals were killed at varying intervals thereafter, and blocks of tissue taken from the stomach and skin. Microscopic examination showed that the Schwartzman phenomenon occured in the stomach wall and that the severity of the reaction is in general parallel to that of the skin.

Schwartzman Phenomenon in the Knee Joints of Rabbits. Moretz, A. R., and Morley, J. D.: Ibid., 321.

The Schwartzman phenomenon was applied to the knee joints of 11 rabbits. Filtrates from cultures of *B. coli* and *B. typhosus* were used. Skin injections were made simultaneously with those in the joints. In 6 rabbits the phenomenon was elicited in the joints. The reactions obtained did not always parallel those in the skin. Results were determined by microscopic examination of tissue sections. Attempts to elicit the reaction in pleural and peritoneal cavities were unsuccessful.

Comparative Protective Efficacy of Some Barbitals Against the Symptoms of Anaphylactic Shock. Hurwitz, S. H., and Wessels, A. L.: Ibid., 1016.

It is well known that certain depressants of the central nervous system are effective in preventing anaphylactic shock. The efficiency of some of the barbitals was tested for this purpose. Amytal, phenobarbital and barbital were used. Guinea pigs were sensitized with horse serum, and the shocking dose was given two to three weeks later with typical shock in most of the control animals.

The sodium salts of the barbitals were administered intramuscularly in large doses about twenty minutes before the shocking dose. About 90 per cent of those having received amytal died from shock within five minutes. Of those treated with barbital 77 per cent died. Only 22 per cent of those who had received phenobarbital succumbed.

Observations in man with phenobarbital were made in a few cases. The oral administration of the drug has been found to prolong the relief from the symptoms of bronchospasm obtained by epinephrine or ephedrine. A combination of ephedrine and phenobarbital has been found

particularly useful in the intractable asthmatic who reacts unfavorably to ephedrine products.

A Nonspecific Cutaneous Sensitivity Which Is Passively Transferable With the Serum to the Normal Human Skin. Walzer, M.: J. Immunol. **23**: 99, 1932.

In the testing by the indirect method, i. e., passive transfer, of more than 200 cases of atopic hypersensitiveness, three sera were found which, when injected into normal skins induced a nonspecific hypersensitiveness. The reaction in the sites sensitized by these three sera was greater irrespective of the substances subsequently used for intracutaneous test than the reaction obtained on normal skins by identical substances. This increased reactivity of the sensitized area occurred even when the intracutaneous tests were made with physiologic saline, distilled water or unaltered human serum. This hypersensitiveness persisted for several weeks and diminished very slowly.

The three sera were obtained from asthmatic patients who had suffered from asthma over a considerable period of years and two of whom had also suffered from eczema since infancy.

The conclusion is drawn that a Prausnitz-Küstner passive transfer test cannot be considered positive unless a control test with physiologic saline on one of the sites of injection has ruled out the possibility of a nonspecific hypersensitiveness.

The Anaphylactic Hormone. Editorial, J. A. M. A. **99**: 392, 1932.

There are two hypotheses generally advanced to explain the cellular phenomena of anaphylaxis:

(1) The assumption that the alien protein-cellular conjugation is itself a sufficient stimulant to cause smooth muscle contraction.

(2) The assumption that the specific colloidal cellular conjugation, itself relatively nontoxic, leads to a local explosive formation or liberation of allergic hormones which in turn act as the immediate stimulants.

In support of this latter hypothesis has been the work of Manuaring and his associates on anaphylaxis is the dog, wherein the inference is to be drawn that the smooth muscle contractions in the anaphylactic dog are secondary allergic phenomena, due to histamine-like autointoxicants explosively formed or liberated by the hypersensitive liver.

This work has been confirmed and extended by experiments reported by the Northwestern University research group. The presence of the anaphylactic shock hormone was found in canine thoracic duct lymph. In some instances 0.25 c.c. of this shock lymph added to a 200 c.c. bath of Tyrode's solution was sufficient to throw the isolated guinea pig intestine into typical histamine-like tetanus. In no instance did normal canine lymph, even in large amounts, have any apparent histamine-like effect. Analysis showed the hormone to be thermostable and dialyzable. In-

tradermal injection of the dialysate in the human skin led to the production of a typical allergic wheal. Evidence points to the assumption that this canine lymphatic anaphylactic hormone is identical with histamine or that histamine is its dominant component.

Other workers have found a similar phenomenon to occur in the anaphylactic guinea pig. German investigators estimate the amount of histamine explosively formed or liberated by the hypersensitive guinea pig lung transfused with Tyrode's solution plus specific foreign protein, to be 0.0005 to 0.0040 mg. They also are of the opinion that the shock hormone is identical with histamine and attribute solely to it the bronchoconstriction of guinea pig anaphylaxis.

A final conclusion as to the importance of explosive histaminemia in human anaphylaxis cannot be drawn from the foregoing experiments, but the evidence in favor of a secondary anaphylactic toxin is conclusive.

Book Review

ALLERGIE ET ANERGIE EN CLINIQUE. V. DE LAVERGNE. Pp. 312, 1931, Gaston Doin, Paris.

This volume is of interest to us in America because of its theoretical and to a lesser extent clinical considerations of the related conditions—allergy and anergy. In his discussion of allergy, the author states that it is synonymous with anaphylaxis and that it probably includes anaphylactoid, idiosyncratic and colloidoclassic reactions. The fundamental problems of allergy are emphasized through his discussion of bacterial sensitization, especially in relation to tuberculosis, glanders, smallpox, malta fever, typhus, gonorrhea, syphilis and other infections. He feels that group sensitizations to bacteria are common. He points out that monovalent allergy frequently leads to a polyvalent type and that cold, shock and emotions are prone to initiate allergy for which they are not fundamentally responsible. Allergy is intensified by repetition of contacts with the specific antigen and reinjection of serum is liable to produce the Arthus phenomenon. He states that allergy is usually generalized in infections whereas with inhalant or ingestive allergy localization in certain tissues is liable to occur.

The scratch (Von Pirquet), the intradermal (Mantoux), the ocular-conjunctival (Wolff-Eisner) and the passive transfer (Prausnitz-Küstner) tests for allergy are discussed. It is pointed out that specific desensitization was first suggested by Besredka. The Italian school found skin reactions most active in the cutaneous segment, corresponding to the seat of the tuberculosis.

The author theorizes that the allergic reaction is due to an antigen-antibody conflict producing disturbances in the equilibrium of colloidal complexes which is complicated by an upset in the function of the vago-sympathetic system. With repeated shocks, the stability of the colloidal complexes decreases so that later even nonspecific shocks may cause reactions.

Anergy is the state of an organism which has lost either temporarily or permanently the power of allergic reaction which it formerly possessed. The organism is thus incapable of defending itself. This idea has not been emphasized in our literature and is in contrast to the idea originally enunciated by C. Richet, that anaphylaxis assures the integrity of the species through foreign protein reactions.

Pregnancy, dehydrated and cachectic states, infections, ductless gland disturbances and organic decadence are productive of anergy. Von Pirquet first noted a disappearance of the tuberculin reaction in measles

and since then most of the knowledge of anergy has been developed through the use of tuberculin and the vaccinal reaction. When anergy exists, secondary infections or relapses of infections are liable to occur. Anergy may last for days or weeks after the original cause has disappeared. It is interesting that the immunity reaction of Schick is not modified by anergy.

The second part of the book discusses in detail the literature and the clinical aspects of the important types of bacterial allergy and will be stimulating to all interested in this field. Serum allergy, bronchial asthma, dermatologic sensitizations, including those due to bacteria and mycoses, are finally considered.

A. H. R.